p-AMINOPROPIOPHENONE AND DERIVATIVES

By

Carroll Pross Foster

Thesis submitted to the Faculty of the Graduate School
of the University of Maryland in partial
fulfillment of the requirements for the
degree of Doctor of Philosophy

1942

UMI Number: DP70113

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Acknowledgement

The author wishes to express to the following his sincere appreciation for the assistance and advice he has received in the completion of this study:

Doctor Walter H. Hartung who suggested the problem and under whose careful supervision and guidance the work was carried out.

Doctor Edgar B. Starkey for his numerous helpful suggestions.

Doctor E. G. Vanden Bosche for his constant encouragement during the course of this investigation.

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INTRODUCTION

Once the chemical structure of epinephrine had been determined, attempts were promplty made to determine whether the molecule in its entirety was necessary for exerting the particular actions of epinephrine.

Much of the ground was cleared by the pioneer work of Barger and Dale (1) in their classical investigation of a large number of synthetic amines, more or less closely related to epinephrine in structure, with a view to determing whether they possess the "sympathomimetic" action, i.e. mimic the sympathetic effect of epinephrine and what is their relative potency compared with epinephrine itself.

Beginning with Barger and Dale numerous experimental contributions from various laboratories have made it possible to establish certain relationships. These may be briefly summarized along the following lines:

Optimum Skeleton

Barger and Dale (1) began with an investigation of simple aliphatic amines. They observed that while simple compounds, such as isoamylamine, possess slight pressor properties, greater activity is found in compounds having an aromatic nucleus. Following their extensive studies on the relationship between chemical structure and physiological action in this series, these scientist concluded; "The optimum carbon skeleton for sympathomimetic activity consists of a benzene ring with a side chain of two carbon atoms, the terminal

one bearing the amino group". These conclusions (1) were based

chiefly on a series of compounds in which the relative positions

of the phenyl and amino groups were varied. Aniline, $C_6H_5-NH_2$,

was without effect, benzylamine, $C_6H_5-CH_2-NH_2$, was slightly active,

α-phenylethylamine, $C_6H_5-CHNH_2-CH_3$, more active. β-phenylethyl-

amine, $C_6H_5-CH_2-CH_2-NH_2$, had maximum activity while γ-phenyl-

propylamine, $C_6H_5-CH_2-CH_2-CH_2-NH_2$, was much less active.

Length of Chain

The ability to produce a rise in blood pressure is resident

in compounds with two or three carbon atoms in the side chain;

derivatives with a two carbon atom chain, $C_6H_5-\overset{|}{C}-\overset{|}{C}-\overset{|}{N}$, are effective

after injection whereas extension of this chain to three carbon

atoms, $C_6H_5-\overset{|}{C}-\overset{|}{\underset{-N-}{C}}-\overset{|}{C}$, gives rise to compounds which are capable of pro-

ducing an effect of longer duration (except in the case of the catechol

derivative), and also possess the added virtue of being potent after

oral administration. These conclusions are substantiated by the re-

sults of Hartung and Munch (2) obtained from four isomeric phenyl-

propyl amines; it was found that

 CH₂-CH-CH₃ with NH₂ below   and   CH-CH₂-NH₂ with CH₃ below

$$\text{(phenyl)}-CH_2-\underset{NH_2}{CH}-CH_3 \qquad \text{and} \qquad \text{(phenyl)}-\underset{CH_3}{CH}-CH_2-NH_2$$
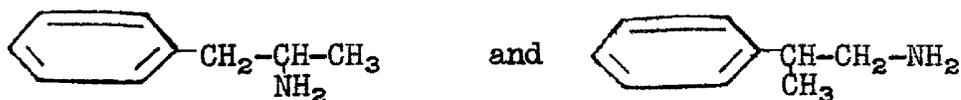
are active after both injection and oral administration; whereas

$$\text{(phenyl)}-\underset{NH_2}{CH}-CH_2-CH_3 \qquad \text{and} \qquad \text{(phenyl)}-CH_2-CH_2-CH_2-NH_2$$

possess slight or negligible pressor activity (3).

Further confirmation of the oral-inactivity of the two-carbon chain and oral-activity of the three-carbon chain is observed by comparing phenylethanolamine, C_6H_5-CHOH-CH$_2$-NH$_2$, and epinephrine, (HO)$_2$C$_6$H$_3$-CHOH-CH$_2$-NHCH$_3$, both ethane derivatives, with ephedrine, C_6H_5-CHOH-CH-CH$_3$, and nor-homoepinephrine, (HO)$_2$C$_6$H$_3$-CHOH-CH-CH$_3$,
       NHCH$_3$ NH$_2$
propane derivatives; the former are inactive on the circulation when given by mouth whereas the latter cause pronounced rises in blood pressure when given orally (4,5,6). Chen, Wu, and Henriksen (6), found such compounds as ephedrine, propadrine, benzedrine, all to be orally active.

However, further extension of the side chain gives results of a negative character (1,8). It was found that phenybutanolamine is slightly active (9). On further lengthening of the side chain, up to phenyloctanolamine, no pressor activity is apparent, the most outstanding change in physiological activity being a regular increase in toxicity. Phenylpentanolamine and its higher homologs when given intravenously provoke a fall in blood pressure.

Alcoholic Hydroxyl

The presence of an alcoholic hydroxyl group on the carbon bearing the aromatic group serves to detoxicate, at lease in part, and to augment the pressor activity (5). There is no evidence to indicate what may be expected if the hydroxyl group is shifted to other positions in the side chain. The effects of the substitution of alcoholic hydroxyl are summarized in Table I.

Table I.

Summary on Alcoholic Hydroxyls
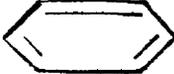
Compound	Pressor Action Epinephrine = 1	Relative Toxicity
⬡—CH$_2$-CH$_2$-NH$_2$ (2,11)	1/350	
⬡—CH-CH$_2$-NH$_2$ (2,11) $\quad$ OH	1/350	Half as toxic as phenylethylamine
⬡—CH$_2$-CH-CH$_3$ (2,11) $\qquad$ NH$_2$ (Benzedrine)	1/350	
⬡—CH-CH-CH$_3$ (2,11) $\quad$ OH NH$_2$ (Propadrine)	1/80	One third as toxic as benzedrine
HO—⬡—CH$_2$-CH$_2$-NH-CH$_3$ (7,11,13)	1/150	
HO—⬡—CH-CH$_2$-NH-CH$_3$ (7,11,13) $\quad$ OH (Synephrine)	1/35	Less toxic than simple amine
HO, HO—⬡—CH$_2$-CH$_2$-NH-CH$_3$ (11,12) (Epinine)	1/12	
HO, HO—⬡—CH-CH$_2$-NH-CH$_3$ (11,12) $\quad$ OH (Epinephrine)	1	
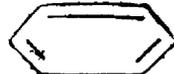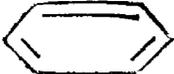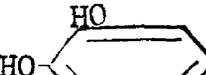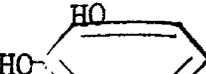
Aminoketones

If the secondary alcoholic group in the aminoalcohols is
oxidized, the corresponding ketonic derivative is obtained. While
our knowledge of pharmacodynamic relationships between the amino-
ketones and the corresponding amino alcohols leaves much to be
desired, all the evidence now available shows that the ketones are
much less active pharmacodynamically. An example of such a case is
adrenalone (5), the ketone corresponding to epinephrine, which has
a much weaker action than epinephrine.

$$HO-\langle\ \rangle-CO-CH_2NH-CH_3 \quad \xrightarrow[1\ :\ 300]{1\ :\ 200} \quad HO-\langle\ \rangle-CH(OH)CH_2-NH-CH_3$$
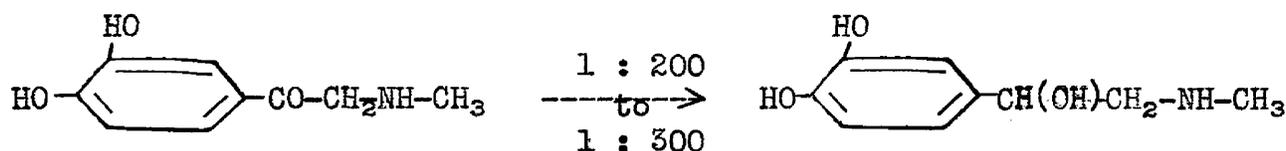
N-alkylation

Substitutions in the amino group result in a decrease of
activity, this indicates that the primary bases are the most active
in their effect on the blood pressure (1,7). Conversion into the
corresponding secondary amine has a tendency to decrease the pressor
activity, the effect increasing with the size of the alkyl group,
and with large alkyl substitution the "sympathomimetic" property
disappears and a depressant action takes its place (7). The corres-
ponding tertiary amines are still much less active, while conversion
into the quaternary ammonium derivative, removes all pressor activity
and confers nicotine-like properties. In general, modification of
the amino group tends to decrease the pressor activity and increase
the toxicity (1). These effects are summarized in Table II.

Table II.

Summary of N-alkylation
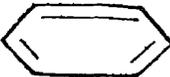
Compound	Pressor Action Epinephrine = 1	Relative Toxicity
⬡–CH_2–CH_2–NH_2 (5,7,11)	1/350	
⬡–CH_2–CH_2–NH–CH_3 (5,7,11)	1/350	Toxicity doubles on substitution
⬡–CH(OH)–CH_2–NH_2 (5,11,14)	1/350	
⬡–CH(OH)–CH_2–NH–CH_3 (5,11,14)	1/700	Toxicity about same
⬡–CH(OH)–CH–CH_3 (5,11,14) NH_2	1/80	
⬡–CH(OH)–CH–CH_3 (5,11,14) NH–CH_3	1/95	50% more toxic than primary amine
⬡–CH(OH)–CH–CH_3 (5,11,14) $N(CH_3)_2$	1/600	
⬡–CH(OH)–CH–CH_3 (5,11,14) NH–C_2H_5	1/150	Toxicity increases with alkylation
⬡–CH(OH)–CH–CH_3 (5,14) NH–C_3H_7	Depressor	
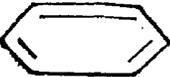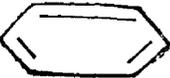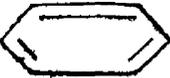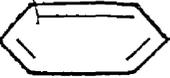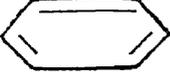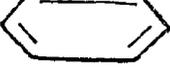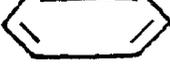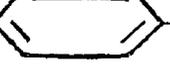
Table II.   (Cont.)
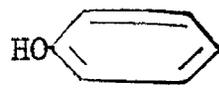
Compound	Pressor Action Epinephrine = 1	Relative Toxicity
HO—⟨benzene ring⟩—CH_2–CH_2–NH_2 (5,14) Tyramine	1/150	
HO—⟨benzene ring⟩—CH_2–CH_2–NH–CH_3 (5,14)	1/150	
HO—⟨benzene ring⟩—CH_2–CH_2–$N(CH_3)_2$ (5,14)	1/700	Toxicity increases with alkylation
HO—⟨benzene ring⟩—CH_2–CH_2–NHC_2H_5 (5,14)	1/200	

Phenolic Hydroxyl

Barger and Dale (1) were the first to investigate the role of the phenolic hydroxyl group. Their results supplemented by the work of Alles and Tainter (10), show that the intensity of action of phenolic pressor substances is much greater than that of the corresponding non-phenolic compounds. Barger and Dale (1) compared the three monophenols of β-phenylethylamine and observed that the ortho-derivative, $HO\text{-}C_6H_4\text{-}CH_2\text{-}CH_2\text{-}NH_2$, was no more active, but more toxic, than the phenylethylamine, $C_6H_5\text{-}CH_2\text{-}CH_2\text{-}NH_2$, itself. Whereas the $m\text{-}HO\text{-}C_6H_4\text{-}CH_2\text{-}CH_2\text{-}NH_2$ and $p\text{-}HO\text{-}C_6H_4\text{-}CH_2\text{-}CH_2\text{-}NH_2$ compounds were about five times more potent than the parent amine. However, the meta-substitution increased the toxicity while the para-substitution lowered the toxicity. They found 2,3,4-trihydroxyphenyl-methylaminomethyl ketone, $(HO)_3{\equiv}C_6H_2\text{-}CO\text{-}CH_2\text{-}NHCH_3$, to be less active than 3,4-dihydroxy-phenyl-methylaminomethyl ketone, $(HO)_2{=}C_6H_3\text{-}CO\text{-}CH_2\text{-}NHCH_3$, showing that the introduction of the third phenolic hydroxyl group decreases activity. Maximum activity was found in 3,4-dihydroxy-derivatives. From these results Barger and Dale concluded that the meta- and para-hydroxyl groups are of equal influence and that maximum activity results if both are present.

However, later workers, notably Tainter (10) and Schaumann (5) have demonstrated that the effect of meta- and para-hydroxyl substitution differs not only quantitatively but also qualitatively. For example, propadrine is musculotropic whereas 3,4-dihydroxy-propadrine (nor-homo-epinephrine) is sympathicotropic. In the structural transition from propadrine to its 3,4-dihydroxy deriv-

ative, it was found that introduction of the para-hydroxyl still

leaves the compound predominantly musculotropic, whereas intro-

duction of the meta-hydroxyl forms a compound which shows definite

but incomplete sympathicotropic activity. These changes may be

schematically summarized as follows:

(m-hydroxypropadrin)

predominantly musculotropic

(propadrin)

musculotropic

(3,4-dihydroxypropadrin)

completely sympathicotropic

(p-hydroxypropadrin)

much more but not completely
sympathicotropic
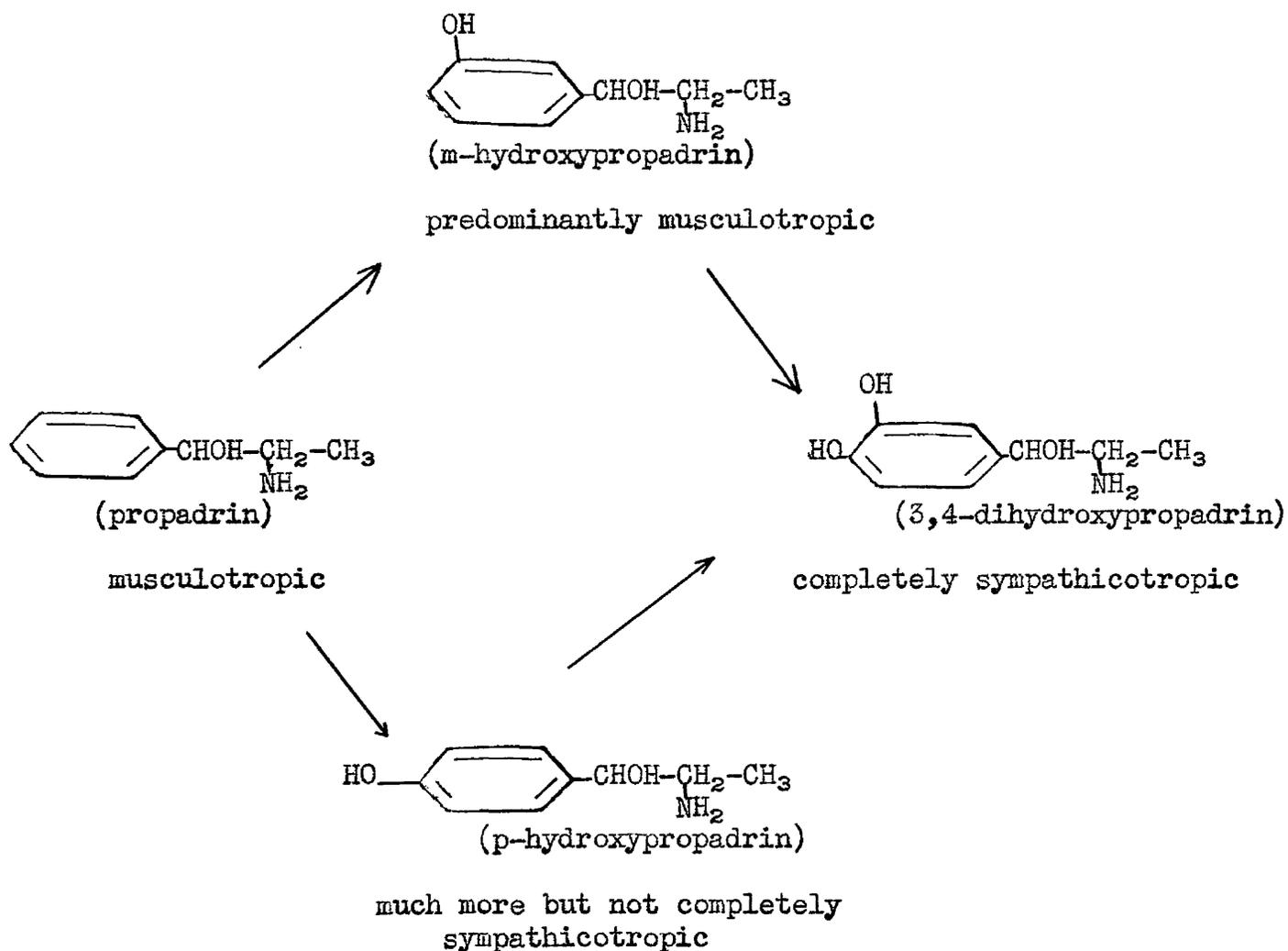
The above and other similar compounds are summarized in Table III.

Table III.

Effect of Phenolic Hydroxyls

Compound	Pressor Activity Epinephrine = 1	Relative Toxicity
(I) [benzene ring] CH₂-CH₂-NH₂ (1,5,10)	1/350	
[benzene ring with OH] CH₂-CH₂-NH₂ (1,5,10)	1/350	More toxic than I.
[benzene ring with OH] CH₂-CH₂-NH₂ (1,5,10)	1/70	More toxic than I.
[benzene ring with OH para] CH₂-CH₂-NH₂ (1,5,10) Tyramine	1/150	Less toxic than I.
[benzene ring with two OH] CH₂-CH₂-NH₂ (1,5,10)	1/35	Toxicity only slightly more than I.
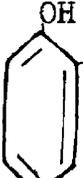
Table III.   (Cont.)

Compound	Pressor Activity Epinephrine = 1	Relative Toxicity

(II)

$CH-CH_2-NHCH_3$ (1,5,10) Synephrine   1/35

$CH-CH_2-NHCH_3$ (1,5,10) Neo-synephrine   1/5   More toxic than II.

$CH-CH_2-NHCH_3$ (1,5,10) Epinephrine   1   More toxic than II.

(III)

$CHOH-CH-CH_3$ (1,5,10) Propadrine   1/80
NH_2

Table III.   (Cont.)

Compound	Pressor Activity Epinephrine = 1	Relative Toxicity

OH

CHOH–CH–CH$_3$ (1,5,10)
$\quad\;$ NH$_2$

1/50

One third as toxic as III.

OH

CHOH–CH–CH$_3$ (1,5,10)
$\quad\;$ NH$_2$

1/25

Three times as toxic as III.

OH
$\quad$ OH

CHOH–CH–CH$_3$ (1,5,10)
$\quad\;$ NH$_2$ (Cobefrine)

1/4

One one-hundredths as toxic as Epinephrine.

Schaumann (5) suggests a gradual change from a musculotropic action to sympathicotropic action as the substitution of a single phenolic hydroxyl group is shifted from ortho to para to meta, the simultaneous introduction of both the meta- and para-hydroxyls conferring sympathicotropic reaction.

Other Substituents in the Aromatic Nucleus

(1) Methyl group. Hartung and Munch (5,15,16) found that a methyl group substituted in the para-position of phenylpropanolamine, decreases the pressor activity about 3/5ths and increases toxicity about threefold. If a methyl group is substituted in the meta-position of phenylpropanolamine, it seems to increase toxicity as much as does a methyl group in the para-position and at the same time decreases pressor activity.

The intorduction of a methyl group into phenolic derivatives of phenylpropanolamines produced the following results: 3-methyl-4-hydroxyphenylpropanolamine is about twice as active and about four times as toxic as phenylpropanolamine (5).

$$\begin{array}{c} OH \\ \text{CH}_3 \\ \bigcirc \\ CHOH-CH-CH_3 \\ NH_2 \end{array}$$
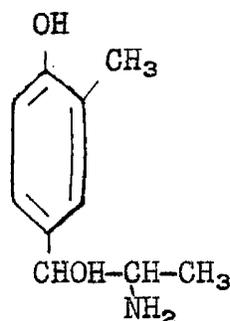
Its isomer, 3-hydroxy-4-methylphenylpropanolamine, while equally as active, was much less toxic than phenylpropanolamine itself, which

is just the opposite to p-methyl substitution alone (5).

$$CH_3$$
$$OH$$
$$H-\underset{OH}{\overset{}{C}}-\underset{NH_2}{\overset{H}{C}}-CH_3$$
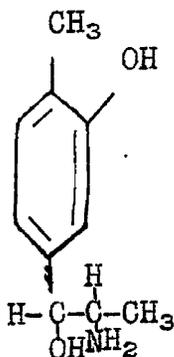
Since the substitution of either the para-methyl or the meta-hydroxyl alone increases the toxicity severalfold, it seems as if the simultaneous introduction counteracts their individual toxic effect.

(2) Methoxyl Substitution. In the arylpropanolamine series several methoxy compounds have been prepared and studied by Hartung, Munch, Miller and Crossley (5).

The ortho-derivative, $CH_3O-C_6H_4-CHOH-CH(NH_2)-CH_3$, was as active but more than twice as toxic as phenylpropanolamine. The para-methoxy isomer is twice as toxic and the pressor activity is one half that of phenylpropanolamine. Another interesting compound was the 2,3-dimethoxyphenylpropanolamine which is as active but more than three times as toxic as phenylpropanolamine.

Another β-phenylethylamine substance that is of unusual interest is the 3,4,5-trimethoxy-derivative known as mescaline.

$$OCH_3$$
$$CH_3O \qquad OCH_3$$
$$CH_2-CH_2-NH_2$$
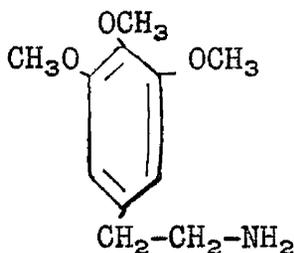
It has been reported as having practically no effect on the blood pressure (17).

(3) Miscellaneous Para-Substituents. Tainter (17a) investigated a series of para-substituted β -phenylethylamines and reported the following:

Para Compound $R-C_6H_5-CH_2-CH_2-NH_2$	Pressor Activity Epinephrine = 1
where R =	
-COOH	inactive
-COOC$_2$H$_5$	1/900
-NO$_2$	1/823
-Cl	1/368

Amino Substitution

The effect produced on the physiological properties of compounds of the epinephrine-ephedrine series by the introduction of an amino group into the aromatic portion of the molecule has received some attention(18). The substances, para aminoephedrine, "Ephetonal", (18,19,21,29)
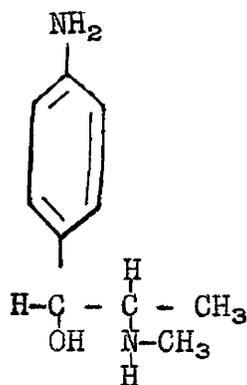
and para-aminopropadrine, (22,23)

$$NH_2$$

$$H-C - \overset{H}{\underset{NH_2}{C}} - CH_3$$
$$OH$$
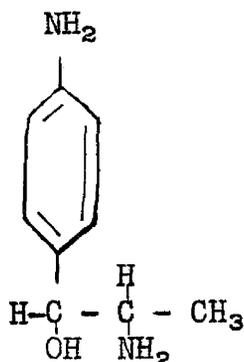
and meta-aminopropadrine, (24,25)

$$NH_2$$

$$H-C - \overset{H}{\underset{NH_2}{C}} - CH_3$$
$$OH$$
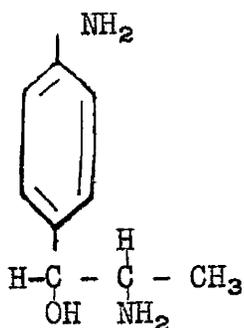
have been prepared synthetically but of the three only"Ephetonal"
appears to have received any study.

"Ephetonal" is described as a white powder (20,26,27), the
free base melting at 114° to 116° C. , the monohydrochloride melt-
ing indefinitely at 175° C. It is reported that, "Its pharma-
cological effect differs from that of ephedrine in that the extent
of its so called sympathetic action is greater, but unlike ephedrine,
it does not exhibit tachyphylaxis nor do large doses produce a de-
pression in the blood pressure" (20). While no comparative study
of para-amino and para-hydroxy has been reported, it would seem that

the two possess remarkably similar properties. "This means that the typical action of this drug on the sympathetic system does not change to the opposite effect, as in the case of ephedrine when the dose is increased or repeated. Furthermore this compound is described as being one third to one half as toxic as ephedrine" (20). This drug is used in same manner as ephedrine. Tainter refers to this drug, as a compound which has been introduced into clincial medicine without adequate experimental data (28,29). The therapeutic properties of meta-aminopropadrine are said to compare favorably with thoseof "Ephetonal"(24,25).

Para-aminopropadrine, a synthetic compound, is reported to possess an ephedrine-like action. This compound appears to have inadequate pharmacological background.

These amino compounds, however, deserve more attention than they seem to have received thus far. For instance, the amino group, according to Franklin (30), is the ammono-analog of the hydroxyl group, and like the hydroxyl group when introduced into an organic molecule (31), confers lyophilic properties. It should prove enlightening to learn whether these structurally "isosteric" substituents produce identical or similar modifications in the physiological reactivity. It should prove interesting and not unexpected to find considerable parallelism between the properties and activities of, for example, para-hydroxy- and para-aminopropadrine. Will meta-aminopropadrine, like meta-hydroxypropadrine, take on greater sympathicotropic behavior? Will complete sympathicotropic responses be possible with compounds such as
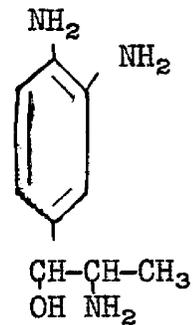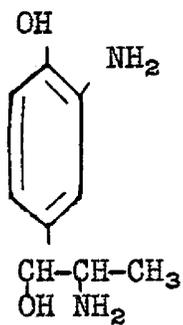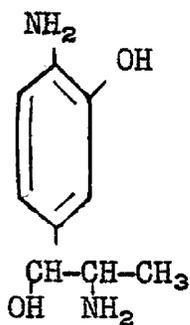
With a desire to obtain an answer to at least some of these questions, the synthesis of para-aminopropadrine was first undertaken. This compound has been synthesized by Oberlin (24,25), but his procedure appears to be inefficient and employs expensive starting materials.

OBERLIN'S PREPARATION OF PARA-AMINOPROPADRINE

Oberlin, in 1929, was first to describe the preparation of para-aminopropadrine as follows:

" 1-Phenyl-2-amino-propanol-1, 20 g., is added to a cooled mixture of 29 ccm. sulfuric acid (sp.g.=1.84) and 30 ccm. nitric acid (sp.g.=1.4); care should be taken that the temperature does not exceed 10° C. After solution has taken place, the mixture is poured on 50 g. ice. The precipitate is separated by filtration and washed with ice-water. Thereby 17 to 18 g. nitrate are obtained which are dissolved in water. Caustic soda is then added to the aqueous solution and the free base, 1-(para-nitrophenyl) 2-amino-propanol-1, is extracted with ether. About 6 or 7 g. of the base are obtained. It is difficultly soluble in ether. The product is converted into the hydrochloride by the addition of an ether solution of hydrochloric acid to an alcoholic solution of the base. The hydrochloride melts at 235° to 240° C. In aqueous-alcoholic solution this product is reduced by means of catalytic hydrogenation e.g. in presence of palladium oxide. The temperature during the hydrogenation should be between 0° to 60° C. After the hydrogenation has been finished (which may be taken from the fact, that no more hydrogen is absorbed), the solution is evaporated to dryness, the residue is taken up with alcohol; this solution is mixed with ether. Thereby the monohydrochloride of the 1-(para-aminophenyl)-2-amino-propanol-1 is obtained; it is white crystalline substance which melts with decomposition between 190° to 192° C. By adding alkali to a solution of the mentioned chloride, the free base may be obtained, which is easily soluble in alcohol,

less easily soluble in ether and insoluble in petrolether. The

precipitated base is taken up with ether. By introducing gaseous

hydrochloric acid in the dried etheric solution, the dihydrochloride

is precipitated. By recrystallizing from alcohol-ether the di-

hydrochloride of 1-(para-amino-phenyl)-2-amino-propanol-1 is ob-

tained in form of shiny, small leaves of a melting point of 192° to

193° C. (dec) yield 1.5 g.".

It will be seen from Oberlin's directions (22) that the reactions

take place substantially as follows:

	NO$_2$	NH$_2$(HCl)
CHOH-CH-CH$_3$ NH$_2$	CHOH-CH-CH$_3$ NH$_2$	CHOH-CH-CH$_3$ NH$_2$(HCl)
20 g. (0.13 mole)	6 or 7 g.(0.03 mole)	1.5 g. (0.006 mole)
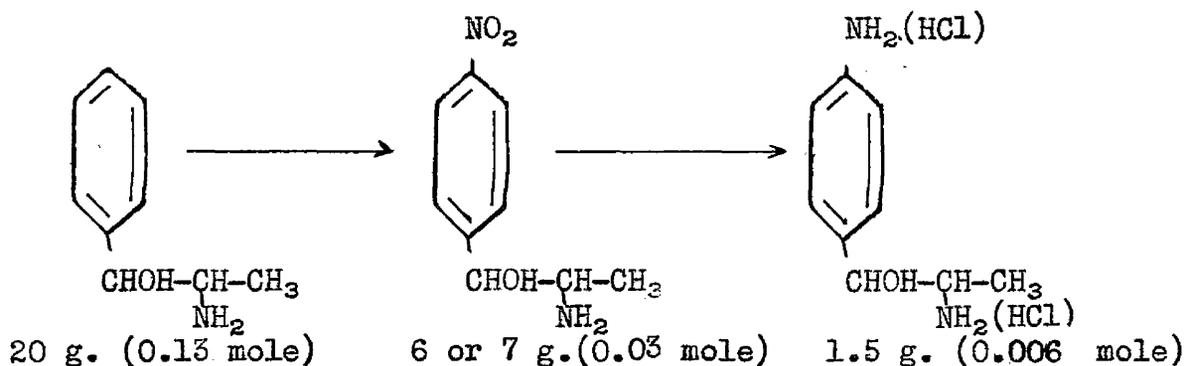
And the reported over-all yield is less than 5%.

This procedure leaves much to be desired as a satisfactory

method for the preparation of para-aminopropadrine. In the first

place the important starting material, phenylpropanolamine, is not

so easily obtained as one would perhaps expect from this method.

The use of sulfuric and nitric acid tend to act somewhat as an un-

controllable oxidizing agent which causes low yields and the formation

of undesirable side reactions. The actual yield for this suggested

preparation of the dihydrochloride of para-aminopropadrine from phenyl-

propanolamine is 4.8%. There is still somewhat of a doubt as to

whether the

$$- \overset{\text{H}}{\underset{\text{OH}}{\text{C}}} - \overset{\text{H}}{\underset{\text{NH}_2}{\text{C}}} - \text{CH}_3$$
group tends to direct only to
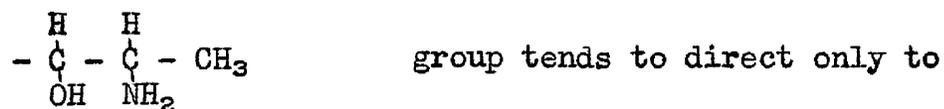
the para position. However, the $- \overset{}{\underset{\text{O}}{\text{C}}} - \overset{}{\underset{\text{NH}_2}{\text{CH}}} - \text{CH}_3$, group, which might

be obtained by the oxidation of the alcohol, tends to direct to the

meta position when treated with the same reagents and using similar

conditions as the author uses.

PROPOSED METHODS FOR SYNTHESIS OF p-AMINOPROPADRINE

In the present investigation the object is to study the preparation of p-aminopropadrine according to the following routes:

NH_2

NH_2
$CO-C_2H_5$

N_2BF_4
$CO-C_2H_5$

$NH-CO-CH_3$
$CO-C_2H_5$

$NH-CO-C_6H_5$
$CO-C_2H_5$

NO_2
$CO-C_2H_5$

$NH-CO-CH_3$
$CO-C-CH_3$
NOH

$NH-CO-C_6H_5$
$CO-C-CH_3$
NOH

NO_2
$CO-C-CH_3$
NOH

$NH-CO-C_6H_5$
$CH-CH-CH_3$
$OH\ NH_2$

$NH-CO-CH_3$
$CH-CH-CH_3$
$OH\ NH_2$

NH_2
$CH-CH-CH_3$
$OH\ NH_2$
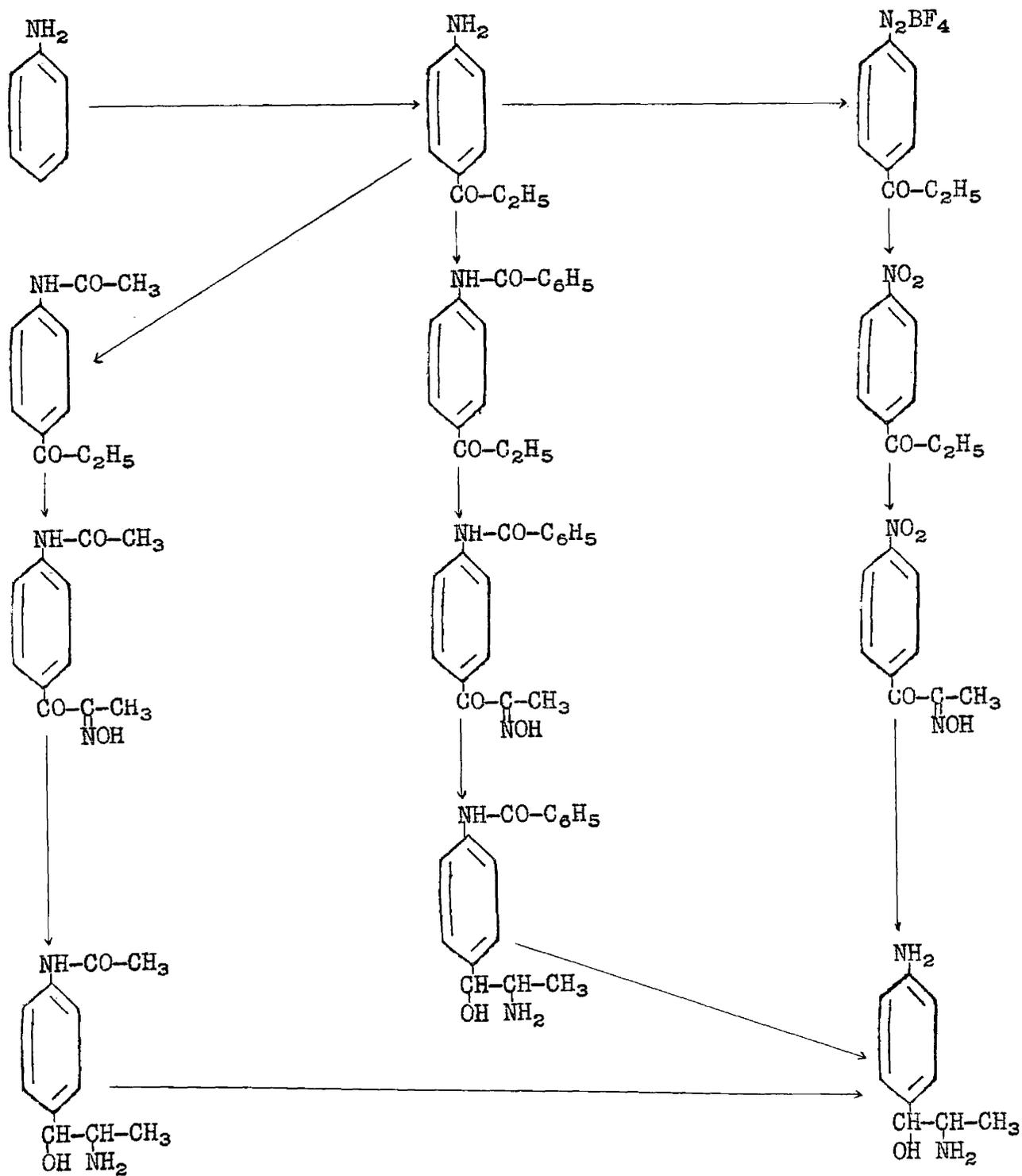
EXPERIMENTAL

Synthesis of p-Aminopropiophenone

Previous studies. Kunckell (32),in 1900, was the first to describe the preparation of p-aminopropiophenone. "Ten grams of acetanilide and 15 grams of propionyl chloride were dissolved in 30 cc of carbon disulfide to which solution was added 20 grams of aluminum chloride in small portions. The mixture was heated for an hour and a half upon the steam bath. The dark red syrup resulting was poured into fine ice, whereupon a brown substance was precipitated. This product was p-acetylaminopropiophenone, m.p. 161° C. (cor). It was hydrolyzed with hydrochloric acid and the p-aminopropiophenone separated by making the solution alkaline. It was purified by crystallization from hot water and when pure, melted at 140° C.(cor)".

This preparation was further studied by Derick and Bornemann (33), who recorded a melting point of 167° C.(cor) for the p-acetylamino-propiophenone.

Hartung and coworkers (34) also repeated Kunckell's work and obtained a melting point of $165-6^\circ$ C.(cor) for the acetylaminopropio-phenone. The analysis, however, indicated that the product might be a mixture of the propionylamino and acetamino-propiophenone.

Found N (Kjeldahl)	6.87% N
Theory for $CH_3-CO-NH-C_6H_4-CO-C_2H_5$	7.33% N
Theory for $CH_3-CH_2-CO-NH-C_6H_4-CO-C_2H_5$	6.82% N

This could easily have taken place as such from their reaction.

NH-CO-CH₃ (ring) + C₂H₅-CO-Cl ——————→ N: -CO-CH₃ / -CO-C₂H₅ (ring) + N: -CO-C₂H₅ / -CO-C₂H₅ (ring)

AlCl₃ ——————→ NH-CO-CH₃ (ring) CO-C₂H₅ + NH-CO-C₂H₅ (ring) CO-C₂H₅
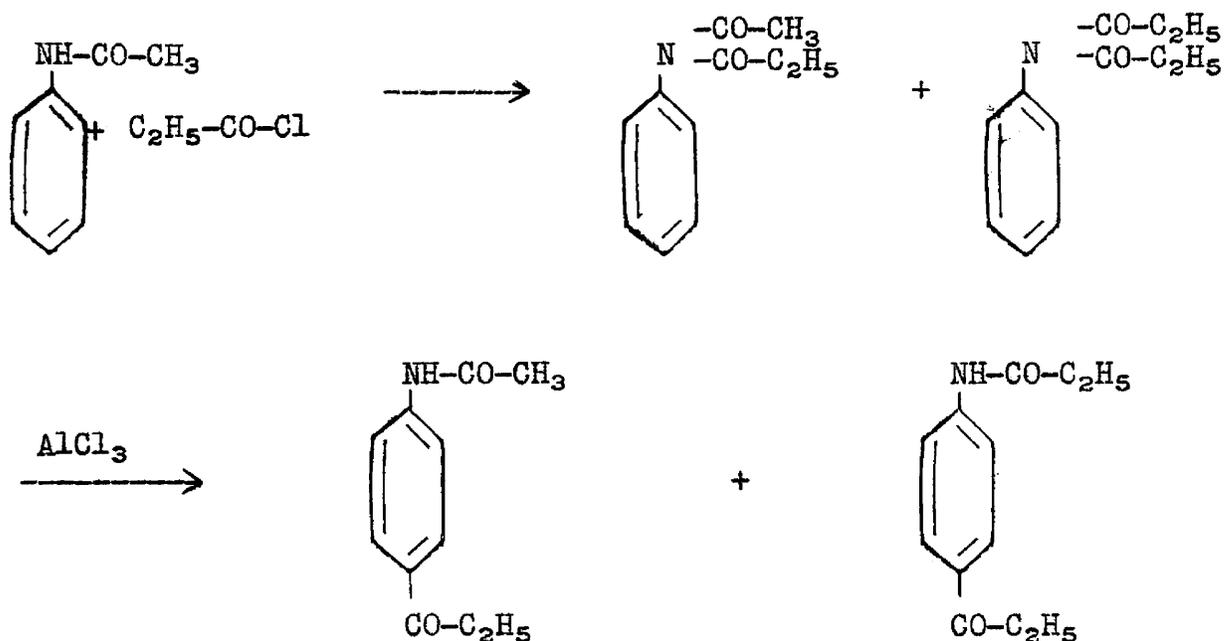
However, for further proof of this, the supposed mixture of acetyl-amino- and propionylamino-propiophenone was hydrolyzed and the pure p-aminopropiophenone with a melting point of 140° C.(cor) was obtained. The p-aminopropiophenone on acetylation and purification gave p-acetaminopropiophenone with melting point of 171.5° C.(dec) (34).

Since this adaptation of the Fries rearrangement seemed to be most applicable for the synthesis of p-aminophenyl ketones of general structure NH₂-C₆H₄-CO-R, it was felt that this reaction deserved closer investigation. In this instance the synthesis of p-amino-propiophenone was repeated approximately fifty times, varying the nature and amount of solvent, the time of reaction, temperature, condensing agent, ratio of reagents and order of their introduction to the reaction chamber, in order to determine optimum conditions.

It is not improbable that these conditions will be equally valid for the synthesis of the homologs of p-aminopropiophenone.

Probably the most important problem in the control of this reaction may be expressed in one word "homogeneity". No other single factor appears to exert such an important influence on the reaction. It is recognized that excess heating or high temperatures will affect adversely the yields and quality of the product. However, deleterious effects may rise if the reaction is allowed to proceed with insufficient or inefficient agitation.

Influencing Factors

Effect of Solvent Ratio. The solvent functions here merely as an inert medium for producing homogeneity. However, enough of it must be employed to produce a homogeneous solution or suspension of the reagents.

The experimental data, assembled in Table IV, show that the actual volume of the solvent employed has a direct effect on the yields. If only a small amount of solvent is employed, the desired "homogenity" is lost, and rather lumpy suspension results which apparently prevents the rearrangement from proceeding smoothly, and low yields follow (expts.1,2,3,35). If sufficient solvent is used, the desired "homogenity" is gained, so that nearly all the material is in solution or in a finely divided suspension, then the reaction proceeds smoothly and better yields result (expts.36,37). If no solvent is used, the reaction mass becomes plastic and very hard to stir, charring takes place and low yields of product are obtained (expts.10,11,12).

Table IV.

Comparison of Quantity of Solvent Employed

Expt. No.	Reaction Time (in hrs.)	Reaction Temp. (°C.)	Solvent	Solvent Ratio[a]	Yield %
1	6.0	46	Carbon Disulfide	0.51	10.0
2	6.0	46	Carbon Disulfide	0.25	5.0
3	6.0	46	Carbon Disulfide	0.41	7.0
35	3.5	46	Carbon Disulfide	0.58	11.1
36	3.5	46	Carbon Disulfide	0.63	23.2
37	3.5	46	Carbon Disulfide	0.66	23-24
10	6.0	25	–	–	3.0
11	6.0	45-46	–	–	less 1.0
12	6.0	90-100	–	–	4.5

a – Parts of solvent per part of total reaction mixture.

NOTE: Aluminum Chloride was added to reaction flask in the beginning.

Effect of Different Solvents. The solvents employed in the study of this reaction were carbon disulfide, nitrobenzene and tetrachlorethylene. The data are summarized in Table V. Of the three solvents tried, carbon disulfide (expts. 20,37,42) seems to be by far the most desirable as a reaction medium. The nitrobenzene (expts.4,26) while a good solvent, has certain disadvantages, chiefly that it must be removed by steam distillation, thereby causing excess heat to be applied to the dissolved products; nor were the yields as good as with carbon disulfide. The tetrachlorethylene has a higher boiling point than carbon disulfide, but with it (expts.27,30,31) the yields of product were uniformly less satisfactory than with carbon disulfide. However, the effect of temperature has not been ruled out, for experiment 30, carried out at 45-46° C., gave a much better yield than the experiments carried out near the boiling point of tetrachlorethylene.

On the basis of the data given in Table V and also data not here given, the results indicate that carbon disulfide is the best of all the solvents tried.

Condensing Agents. Aluminum chloride was the first well described condensing agent and the one that is by far the most generally used in the Friedel-Crafts and the Fries synthesis. Resublimed aluminum chloride is obtainable commercially in a state of high purity and at a low cost. However, the possibility of using zinc chloride or boron fluoride was also investigated. Summary of experiments on the use of different condensing agents is given in Table VI. Reference to Table VI shows conclusively that of the condensing reagents tried, aluminum chloride (expts.9,10,11,27,29,33,37,40) is

Table V.

Comparison of Solvents

Expt. No.	Reaction Time (in hrs.)	Reaction Temp. (°C.)	Solvent	Solvent Ratio[a]	Yield %
4[b]	3.5	90-100	Nitro-benzene	0.5	5.0
26[c]	6.0	45	Nitro-benzene	0.7	5.0
27[c]	6.0	90-100	Tetrachlor-ethylene	0.7	20.0
31[b]	3.5	90-100	Tetrachlor-ethylene	0.7	11.1
37[b]	3.5	46	Carbon Disulfide	0.66	23-24
20[c]	6.0	46	Carbon Disulfide	0.7	20.0
30[b]	5.0	45-46	Tetrachlor-ethylene	0.7	32.0
42[b]	5.0	46	Carbon Disulfide	0.66	20.0

[a] Parts of solvent per part of total reaction mixture.

[b] Aluminum Chloride was added to reaction flask in the beginning.

[c] Added Aluminum Chloride in divided portions to anilide.

Table VI.

Condensing Agents

Expt. No.	Reaction Time (in hrs.)	Reaction Temp. (^{o}C.)	Solvent	Solvent Ratio[a]	Yield %	Condensing Agent
13[c,d]	3.0	25	–	–	0	Boron Fluoride
14[c,d]	3.0	25	–	–	0	Boron Fluoride
17[c,d]	1.0	160–180	–	–	less 1.0	Boron Fluoride
17A[c]	1.0	46	Carbon Disulfide	0.6	0	Boron Fluoride
16[b]	6.0	90–100	–	–	2.0	Zinc Chloride
28[c]	6.0	90–100	Tetrachlor-ethylene	0.7	3.0	Zinc Chloride
25[b]	25.0	46	Carbon Disulfide	0.7	3.2	Zinc Chloride
21[e]	6.0	180	–	–	less 1.0	–
9[b]	2.0	25	Carbon Disulfide	0.6	5.0	Aluminum Chloride
29[b]	3.5	46	Tetrachlor-ethylene	0.7	12.0	Aluminum Chloride
33[b]	1.75	90–100	Tetrachlor-ethylene	0.7	5.7	Aluminum Chloride
10[b]	6.0	25	–	–	3.0	Aluminum Chloride

Table VI. (Cont.)

Expt. No.	Reaction Time (in hrs.)	Reaction Temp. (°C.)	Solvent	Solvent Ratio[a]	Yield %	Condensing Agent
11[b]	6.0	90–100	–	–	less 1.0	Aluminum Chloride
27[c]	6.0	90–100	Tetrachlor-ethylene	0.7	20.0	Aluminum Chloride
37[b]	3.5	46	Carbon Disulfide	0.66	23–24	Aluminum Chloride
40[c]	5.0	46	Carbon Disulfide	0.66	33–35	Aluminum Chloride

[a] Parts of solvent per part of total reaction mixture.

[b] Condensing Agent added to reaction in beginning.

[c] Condensing Agent added as last ingredient.

[d] Formed only Propionanilide.

[e] Carried out in glass bomb.

best also for the migration in aniline of the propionyl group from the nitrogen to the ring. It appears from present knowledge that one essential feature which the condensing agents must have is a great facility for forming a highly active complex with one or both reactants.

The importance of the migrating agent is further seen in experiment 21, where heat alone was employed to determine whether it might produce rearrangement; it will be seen that the yield of p-aminopropiophenone in this instance is negligible. Therefore, in reactions of this type, the condensing agent appears to increase the rate of reaction, and also makes it possible to carry out the synthesis at a lower temperature (39).

Neither zinc chloride (expts.16,25,28) nor boron fluoride (expts. 13,14,17,17a) gave encouraging results, although they were tried with various solvents and at different temperatures (Table VI).

The next question is to determine the effect of the order of feeding the materials into the reaction vessel. Table VII indicates higher yields when the aluminum chloride is added last and in small divided portions. This procedure facilitates the mechanical and operating phases of the reaction and reduces the fume problems to a minimum. In several experiments (33,37,41,42,43) the aluminum chloride was added to the aniline at the beginning and then the propionyl chloride was added intermittenly. In this procedure two reactions may actually take place simultaneously. The aniline and propionyl chloride may react and rearrange, and at the same time, propionyl chloride and aluminum chloride may form complexes (36).

Table VII.

Effect of Order of Adding Materials into the Reaction Vessel

Expt. No.	Reaction Time (in hrs.)	Reaction Temp. (°C.)	Solvent	Solvent Ratio[a]	Yield %
20[c]	6.0	46	Carbon Disulfide	0.7	20.0
43[b]	6.0	46	Carbon Disulfide	0.66	17.0
38[c]	5.0	46	Carbon Disulfide	0.66	34.0
39[c]	5.0	46	Carbon Disulfide	0.66	33.5
40[c]	5.0	46	Carbon Disulfide	0.66	33-35
41[b]	3.5	46	Carbon Disulfide	0.66	15.0
42[b]	5.0	46	Carbon Disulfide	0.66	20.0
37[b]	3.5	46	Carbon Disulfide	0.66	23-24
32[c]	1.6	90-100	Tetrachlor-ethylene	0.7	18.0
33[b]	1.75	90-100	Tetrachlor-ethylene	0.7	5.8

[a] Parts of solvent per part of total reaction mixture.

[b] Aluminum Chloride added to reaction flask in the beginning.

[c] Aluminum Chloride added as last ingredient.

However, if two molecules of propionyl chloride and one molecule of aniline are first allowed to react together, they will form the dipropionylanilide; if the aluminum chloride is added to this compound, the rearrangement proceeds slowly (expts. 20,32,38,39,40) and at no time is there an excess of condensing agent to cause charring. This is in agreement with observations reported by previous workers. Many German references indicate a preference for adding the aluminum chloride last (36).

Effect of Change in Temperature. Temperature seems to have a definite effect on the rate and extent of the reaction. The reaction mixture must be kept at room temperature or below until all of the aluminum chloride is added. Then it is gradually raised on a water bath to 45-46° C., the refluxing point of the carbon disulfide solvent. If the temperature is permitted to rise prematurely, the ketone is contaminated by side-reaction products.

If, the temperature is allowed to rise much above 46° C., the yields are smaller and larger amounts of tar are found. Below 45° C., the reaction must be continued over a longer period of time, and even then smaller yields are obtained. The optimum temperature for this reaction seems to be approximately 45-46° C.

A resumé of data on experiments showing the effect of variation in temperature is given in Table VIII.

Another point of interest is the effect of time of heating at optimum temperature. It was found that heating should be continued until no more hydrogen chloride is evolved. Experience has shown that for a run employing one mole aninline, two moles of propionyl

Table VIII.

Temperature Variation

Expt. No.	Reaction Time (in hrs.)	Reaction Temp. (°C.)	Solvent	Solvent Ratio[a]	Yield %
10[b]	6.0	25	–	–	3.0
11[b]	6.0	90–100	–	–	less 1.0
12[b]	6.0	45–46	–	–	4.5
29[b]	3.5	45–46	Tetrachlor-ethylene	0.7	12.0
31[b]	3.5	90–100	Tetrachlor-ethylene	0.7	11.1
42[b]	5.0	45–46	Carbon Disulfide	0.66	20.0
19[b]	6.0	90–100	Tetrachlor-ethylene	0.6	20.0
23[c]	24.0	25	Carbon Disulfide	0.7	20.0

[a] Parts of solvent per part of total reaction mixture.

[b] Aluminum Chloride added to reaction flask in the beginning.

[c] Aluminum Chloride added as last ingredient.

chloride with two moles of condensing agent at least five hours will

be necessary. Heating over a longer period of time offers no advantage,

and it may cause an increase in the amount of tar formed. However,

no adverse effects were observed if the heating was interrupted,

provided that the total period of heating was sufficient to complete

evolution of hydrogen chloride. If the optimum temperature is not

kept up for this entire period, then an incomplete reaction results.

The data on which these conclusions are based are given in Table IX.

Molar Ratios of Reagents. In order that rearrangement may take

place, two moles of propionyl chloride are theorectically required

for each mole of aniline (33). The amount of aluminum chloride needed

is at least two moles. The propionyl chloride and the aluminum chloride

form complexes of the type R-CO-Cl-AlCl$_3$ (36).

Although the aluminum chloride functions as a condensing agent,

it is not regenerated during the reaction; instead it forms a stable

and inactive complex with the newly formed ketone. Thus the reaction

for the formation of the ketone may be represented by two steps
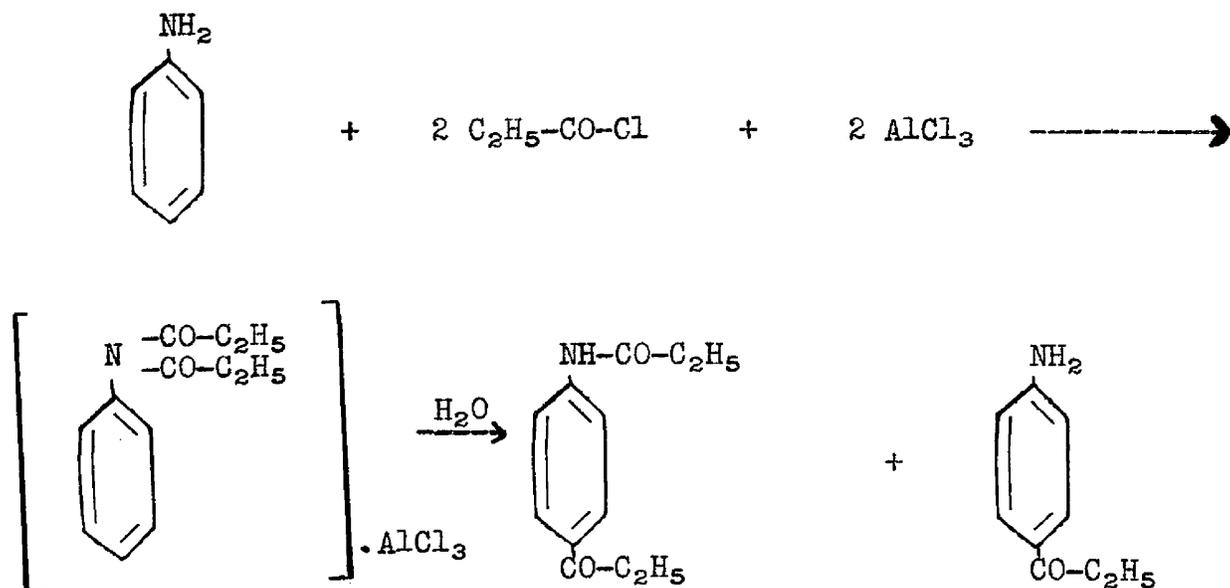
Table IX.

Effect of Changes in Reaction Time

Expt. No.	Reaction Time (in hrs.)	Reaction Temp. (°C.)	Solvent	Solvent Ratio[a]	Yield %
41[b]	3.5	46	Carbon Disulfide	0.66	15.0
42[b]	5.0	46	Carbon Disulfide	0.66	20.0
43[b]	6.0	46	Carbon Disulfide	0.66	17.0
8[b]	12.0	46	Carbon Disulfide	0.7	20.0
22[c]	24.0	46	Carbon Disulfide	0.7	15.0
29[b]	3.5	46	Tetrachlor-ethylene	0.7	12.0
30[b]	5.0	46	Tetrachlor-ethylene	0.7	32.0

[a] Parts of solvent per part of total reaction mixture.

[b] Aluminum Chloride added to reaction flask in the beginning.

[c] Aluminum Chloride added as last ingredient.

The general procedure finally adopted for the preparation of p-aminopropiophenone and employed in the present investigation is as follows:

Into a five liter, three-neck, round-bottom flask fitted with a reflux condenser connected to a gas-absorption trap, a sealed mechanical stirrer and a dropping funnel are placed 139.6 g. (1.5 mols) aniline (b.p.184°-185° C.) and 1600 cc carbon bisulfide. The reaction flask is immersed in a bath of cold water (20°-25° C.) and to the rapidly stirred solution is slowly added drop by drop 277.5 g. (3.0 mols) propionyl chloride (b.p.80° C.).

The dropping funnel is replaced with a small powder funnel and during the course of thirty minutes, 400 g. (3 mols) of aluminum chloride (E.K. and Co. resublimed) is added in 15 g. portions to the rapidly stirred mixture; the hydrogen chloride evolved from the reaction while the condensing agent is added may be removed by keeping the reaction set-up under slightly reduced pressure (water-pump). After all of the aluminum chloride is added, stirring and refluxing of the carbon bisulfide (45°-46° C.) is continued on a water bath, until evolution of hydrogen chloride ceases (approximately 5 hours). The mixture is cooled and surrounded by an ice bath, and while stirring, 100 cc of cold 10% hydrochloric acid added drop by drop, keeping the temperature below 30° C. Then sufficient ice water is added slowly to decompose the complex and dissolve the aluminum chloride. The reaction mixture is filtered with suction and the various layers are allowed to separate in a large separatory funnel. The solid material obtained is saved for later hydrolysis, or, the material

may be recrystallized from hot water; this is para-propionylamino-propiophenone (yellow crystals) m.p. 149-150° C. The material in the separatory funnel is allowed to separate completely forming three layers; the lowest layer, carbon bisulfide, is carefully removed and the solvent distilled; residue may be either recrystallized from hot water to obtain pure para-propionylaminoprophenone, or the crude material may be saved for later hydrolysis. The second or aqueous layer is drawn off and made alkaline with excess 10% sodium hydroxide solution; the liberated solid is collected, recrystallized from 40% alcohol); this is para-aminopropiophenone, yellow crystals, (m.p. 140° C.) The third and top most layer, which contains the bulk of the product, is a thick, orange to black oil, which is hydrolyzed directly as follows:

The material is mixed with at least 500 cc of 15 to 20% hydro-chloric acid and refluxed for two to three hours; charcoal is then added to the boiling solution and an equal volume of water is added and the solution again brought to boiling; then it is allowed to cool before filtering without suction. This cold filtrate is made alkaline with sodium hydroxide (10%); the precipitate is collected on a Buchner funnel, washed with cold water and recrystallized from 40% alcohol, identified as para-aminopropiophenone. The amount of para-propionylaminopropiophenone obtained from the carbon disulfide layer is 2-3%, the aqueous layer furnished 1 to 2% of para-amino-propiophenone and the oily layer 20-25%/of para-aminopropiophenone.

of theoretical yield

The free para-aminopropiophenone may be purified by recrystallization from water or from 40% alcohol. It crystallizes in the form of yellow

needles melting at 140° C. (cor). The base is very soluble in alcohol, chloroform, acetone, dioxane, benzene and ether.

Analysis of Free Base

Found nitrogen (Kjeldahl)	9.30% N	9.34% N
Calculated nitrogen for $C_9H_{11}ON$	9.39% N	

The evidence that the amino group is in the position para to the propionyl is found in the fact that when the compound was converted into the corresponding nitro derivative and subsequently oxidized, p-nitrobenzoic acid was obtained, as is described later.

Hydrochloride of p-Aminopropiophenone. This salt is prepared by two methods:

(a) Into an ethereal solution of the free base is slowly bubbled dry hydrogen chloride, the white precipitate is collected, washed with cold alcohol-ether solution and after drying, melts at 198-199° C. (cor).

(b) To an alcoholic solution of the free base is added concentrated hydrochloric acid, the solution is concentrated on a steam bath and than on standing in a cool place yields needle-like crystals melting at 198-199° C. (cor).

Oxime of p-Aminopropiophenone. About 0.5 g. of hydroxylamine is dissolved in 3 cc of water; 2 cc of ten percent sodium hydroxide and 0.5 g. of the ketone are added. Sufficient alcohol is added to the mixture in order to give a clear solution. The mixture is filtered and warmed for ten minutes. The solution is allowed to cool and stand over night. The solution is made neutral to litmus with concentrated hydrochloric acid, cooled and the crystals which

form are collected. The oxime after recrystallization from dilute alcohol melts at 153-154° C.(cor).

p-Acetaminopropiophenone. Fifteen grams (0.1 mol) p-aminopropiophenone is refluxed with 30 cc (excess) of acetic anhydride for half an hour, allowed to cool, and then 30 cc of cold water is added and the solution brought to boiling. After cooling, the solution is filtered and the precipitate, p-acetaminopropiophenone, is collected on a Buchner funnel, and washed with cold dilute hydrochloric acid, the washings being added to the original filtrate. The product, after recrystallization from water, melts at 172-173° C.(cor) and weighs 15 g. (0.078 mol), representing a yield of 80%. However, the filtrate is made alkaline with 10% sodium hydroxide, cooled and 2 g. of unacetylated p-aminopropiophenone is recovered. Thus the yield of acetylated product based on p-aminopropiophenone actually used is 86%.

Analysis of p-Acetaminopropiophenone

Found nitrogen (Kjeldahl)	7.32% N	7.16%
Calculated nitrogen for $C_{11}H_{13}O_2N$	7.29% N	

Oxime of p-Acetaminopropiophenone. About 0.5 g. of hydroxylamine is dissolved in 3 cc of water; 2 cc of ten percent sodium hydroxide and 0.5 g. of p-acetaminopropiophenone are added. Sufficient alcohol is added to the mixture in order to give a clear solution. The mixture is filtered and then warmed for ten minutes. After the solution stands over night, it is filtered to remove any unconverted p-acetaminopropiophenone. The filtrate is made acid with concentrated hydrochloric acid, is cooled and the crystals which

form are collected. After recrystallization from dilute alcohol, the oxime decomposes at 156-157° C.(cor) and is a white crystalline solid, soluble in alkali and in alcohol and insoluble in water.

p-Benzoylaminopropiophenone. Reflux 15 g. of p-aminopropiophenone (0.1 mole) with 40 cc (excess) of benzoyl chloride for half an hour and then allow to cool. Add 40 cc of water and bring to a boil. The cold solution is filtered and the precipitate of p-benzoylaminopropiophenone is washed with cold dilute hydrochloric acid, the washings being added to the original filtrate. This filtrate is made alkaline with ten percent solution of sodium hydroxide; cooled and a precipitate of 1-2 g. of p-aminopropiophenone is recovered. The p-benzoylaminopropiophenone is recrystallized from alcohol and 20 g. of white crystals, melting at 187-188° C.(cor) are obtained. Yield, allowing for recovery of unbenzoylated compound, is 95%.

Analysis of p-Benzoylaminopropiophenone

Found nitrogen (Kjeldahl)	5.59% N	5.57% N
Calculated for $C_{16}H_{15}O_2N$	5.53% N	

Oxime of p-Benzoylaminopropiophenone. About 0.5 g. of hydroxylamine is dissolved in 3 cc of water; 2 cc of ten percent sodium hydroxide and 0.5 g. of p-benzoylaminopropiophenone are added. Then 15 cc of alcohol is added and the mixture refluxed on a water bath for 45 minutes, filtered, and allowed to stand over night. The solution is filtered to remove any unconverted p-benzoylaminopropiophenone and is then made acid with concentrated hydrochloric acid. It is cooled and the crystals which form are collected and dissolved in ten percent solution of sodium hydroxide and filtered. The filtrate is made

acid with concentrated hydrochloric acid and the precipitate which forms is collected. The oxime, after recrystallization from alcohol, decomposes at 164-165° C. (cor), is a white crystalline solid, soluble in alkali and hot alcohol and very insoluble in water.

p-Propionylphenyldiazonium Borofluoride. Previous work by Starkey, Dunker and Ruddy have demonstrated that the dizaonium borofluorides are superior as intermediates to the diazonium chlorides for the preparation of aromatic mercury compounds (40), aromatic arsonic acids (42,43) and for the substitution of a nitro group for aromatic amino group (41). The diazonium borofluorides are easily prepared and can be isolated and purified before use. The diazotization in fluoboric acid can be carried out in an ordinary ice bath without requiring particular attention as to temperature. The resulting diazonium compounds are obtained in yields up to practically quantitative, and may be washed free from impurities and dried with alcohol and ether. When thoroughly dried and placed in an evacuated desiccator, they may be kept satisfactorily for relatively long periods of time, the stability varying with the individual compound. Hence larger quantities of these intermediates can be prepared and used later at one's convenience. Because of their greater stability the diazonium borofluorides in solution have less tendency to decompose before reacting with the desired compound, and as a result, the amount of tar formation is reduced even when the reaction is carried out at room temperature (40,41).

Starkey's method of diazatization applied to p-aminopropiophenone reacts according to the following equation:

$$\text{(p-aminopropiophenone, NH}_2\text{, CO-C}_2\text{H}_5) + 2\ HBF_4 + NaNO_2 \longrightarrow \text{(N}_2BF_4\text{, CO-C}_2\text{H}_5) + NaBF_4 + 2\ H_2O$$
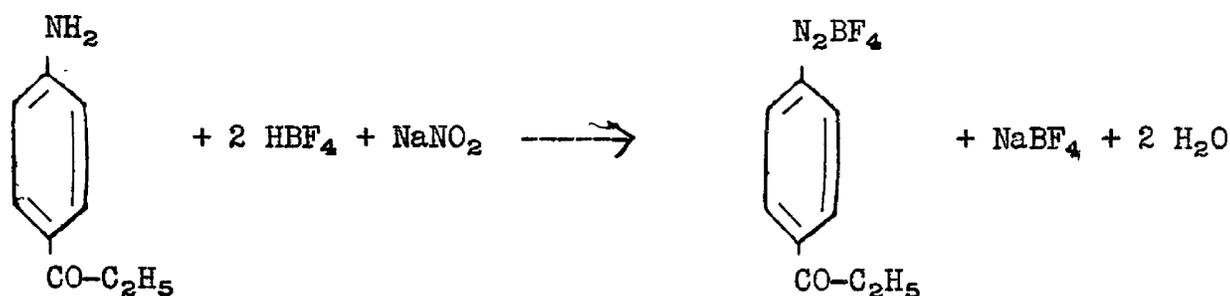
To 43.9 cc (0.25 mole) of 50% fluoboric acid in a 500 cc beaker is

added 14.9 g. (0.1 mole) of p-aminopropiophenone while stirring,

followed by 5 g. of finely divided ice; then a solution of 6.9 g.

(0.1 mole) of sodium nitrite in 15 cc of cold water is added slowly

from a separatory funnel, keeping the temperature of the mixture be-

low 10° C. When the addition is complete, the solid which has formed

is collected on a sintered glass funnel, washed twice with cold alcohol

and then three times with ether and partially dried by drawing air

through it. The resulting brownish crystalline solid is dried over

night in an evacuated desiccator. The yield is 20-22 g., represent-

ing 85% of the theoretical. This diazonium compound decomposes at

85-86° C.

However, it was found that the cost of this preparation could be

reduced and high yields still obtained by substituting a portion of

hydrochloric acid for some of the fluoboric acid. The molecular

ratios found best for the reaction being one mole of the amine (149 g.),

one mole (36.5 g.) of hydrochloric acid (100 cc of concentrated acid),

one and one quarter moles (87.8 g.) of 50% fluoboric acid (220 g.)

and one mole (69 g.) of sodium nitrite dissolved in 150 cc of water.

The diazonium borofluoride, when placed in a dark colored bottle

at room temperature, generates a gas pressure, and over a period of

three weeks, gradually darkens until finally only a tar-like material remains.

p-Propionylphenyldiazonium Chloride. A definite quantity of p-aminopropiophenone is dissolved in an excess of dilute hydrochloric acid. To the dissolved hydrochloride, at room temperature, is added slowly, drop by drop, an aqueous solution of sodium nitrite containing the calculated quantity of nitrite. However, as the nitrite is added, the diazonium chloride is precipitated out of solution. The precipitate is collected, washed with water, alcohol and ether. The dried product is a yellow crystalline solid insoluble in water, alcohol and ether. This salt is stable when dry which is a rather unusual case. Since most references on such compounds will refer to these compounds as crystalline substances and when obtained in a thoroughly dry condition are very explosive, though usually they may be handled with comparative safety when moist. However, this particular dry diazonium chloride could be placed on a hot plate and still no explosion would occur, but merely decomposition.

This diazonium chloride was hydrolyzed with boiling water to yield the p-hydroxypropiophenone. It is recrystallized from water and melts at 147-148° C. These crystals when mixed with some known p-hydroxypropiophenone give no depression in the melting point.

p-Nitropropiophenone: A compound said to be p-nitropropiophenone was described in 1906 by Comanducci and Pescitelli (45,46). A verbatim copy, in part, of their report on the nitration of propiophenone under varying experimental conditions follows:

<u>Riepilogando</u> i metodi di preparazione, abbiamo:

1° <u>Il prodotto fusibile</u> a 85° (probabilmente l'ortoni-troderivato) si ottiene versando il propionfenone sull' acido nitrico al 136% mantenuto a 40°.

2° <u>Quello fusibile</u> a 98° (probablilmente il meta-derivato) si prepara facendo gocciolare il propionfenone sull'acido nitrico al 104% mantenuto a temp. ord. (20°), ma meglio a 4°.

3° <u>Il prodotto fusibile</u> a 114° (forse il para–nitro-derivato si ottiene versando il propionfenone sull'acido nitrico al 104% regolando la temperatura a 40°–60°.

Azione dell'acido nitrico sul propionfenone a temperatura ordinaria ed a caldo.

Versando il propionfennone a goccia a goccia sull'acido nitrico al 104% agitato (temp.ord.20°), si forma lo stesso nitropropionfenone ottenuto a 4° nel modo suddetto con un rendiemtno pero un poco inferiore, Versando il propion-fenone apoco a poco sull'acido nitrico della stessa con-centrazione e scaldate pero a 40° con b.m.,e mantenuto a questa temperature durante l'operazione, si ottenne un liquido rosso-bruno, che versato in acqua, non dette più un composto cristallino, ma un olio denso verdastro, il quale, decantata l'acqua e tenuto in essiccatore ad H_2SO_4 non perde il colore verde che aveva, mentre dibattuto con soluzione di KOH indi con etere e l'estratto etereo seccato su piatto poroso, forni un composto cristallino, bianco-gialletto, fusibile a 114°, solubile nell'acqua calda, in-solubile nell'etere di petrolio, poco nella benzina, sol-ubilissimo invece nell'alcole, etere, cloroformio, benzolo e negli alcali con colorazione gialla. Con soluzione con-centrata di bisolfito sodico da un composto bianco cristallino, che purificato per cristallizzazione dall'acqua è scomposto con H_2SO_4 diluito rida il nitropropionfenone fusibile a 114°.

In una seconda preparazione con HNO_3 della stessa con-centrazione, ma operando ad una temperature di 40°–60° si ottenne un liquido rosso bruno, che versato in acqua dette un abbondante precipitato bianco gialletto, che filtrate e cristallizzato frazionatamente dell'alcole, forni due nitropropionfenoni, uno in propzione dell'80% fusibile a 114°, l'altro in piccola quantità fusibile a 98°. Il filtrato acquoso estratto con etere a freddo dette un ni-troderivato, che cristallizza dell'alcole in piccoli aghi gialletti fusibili a 85°.

Analisi del prodotto fusibile a 114°.

I. gr. 0,1902 di sostanza dettero gr. 0,4186 di CO_2 e gr. 0,0862 di H_2O.

II. gr. 0,1522 di sostanza dettero col metodo Dumas cc.

10,1 di N a 23° e 746,4 mm.Calcolando per 100 si ha:

	Trovato		Calcolato per C_6H_4 $\begin{smallmatrix}NO_2\\CO\end{smallmatrix}$-$CH_2$-$CH_3$
	I	II	
C	60,02	–	60,33
H	5,03	–	5,02
N	–	7,52	7,82

Obviously these authors are in error, except as to m-nitropropio-phenone. Extensive work, frequently repeated, in these laboratories has shown that o-nitropropiophenone is a liquid at ordinary tempera-ture (50,57), and it has been conclusively demonstrated in the present investigation that p-nitropropiophenone is a slightly yellow crys-talline substance melting at 90–91° C. (cor), but never has it been obtained by the direct nitration of propiophenone under any conditions.

Another point of interest is the description by these Italian authors of the nitration of propiophenone, using either 136 percent nitric acid at 40° C. or 104 percent nitric acid at 40–60° C. Not only has it been found impossible to duplicate the results of Comanducci and Pescitelli, but also impossible to operate under the conditions described. It has been found (48) that certain aromatic ketones may be nitrated by adding agitated fuming nitric acid, the temperature being kept preferably below +10° C. It has been further found by various workers (49) that during the numerous and varied attempts to nitrate phenylalkyl ketones, it is impossible to control the nitration reaction at temperatures above 25–30° C. If the tem-perature is allowed to rise higher, the reaction gets out of control, clouds of nitrogen oxide fumes pour out of the reaction flask, and the only organic product to be isolated is m-nitrobenzoic acid. In the light of these experiences it is impossible to see how a tem-

perature of 40-60° C. may be employed under any circumstances.

Fuming nitric acid sp.gr. 1.49-1.50 was found to be most satisfactory in nitrating propiophenone and its homologs. It was also discovered that red fuming nitric acid is less desirable, but works equally well if the fumes are first removed by bubbling air through the acid. These observations seem to conflict with the work of the Italian authors who used "136 percent" and "104 percent" nitric acid which presumably contained excess fumes.

The Italian authors assumed that the product which melted at 114° C. was p-nitro derivative because it had the highest melting point of the three products which they reported. However, as already pointed out, the one product which they called the ortho compound, is described by them as a solid melting at 85° C. This is incorrect for it has been abundantly shown that o-nitropropiophenone is a low melting solid or a yellow oil at room temperature (50,51). While this article suggests a method for proving that the nitro group is in the para-position, it cites no experimental evidence.

Barry (51a) describes two isomeric mononitropropiophenones, obtained by direct nitration. One is characterized as "Syrupartiges Nitropropiophenon" and the other as crystals melting at 100° C. The latter undoubtedly was m-nitropropiophenone (m.p.98° C.cor) and the liquid, o-nitropropiophenone. There is nothing in Barry's report to support the implication by Comanducci and Pescitelli that the crystals may have been p-nitropropiophenone.

p-Nitropropiophenone was prepared in our laboratory by Starkey's method of replacing the diazonium group by the nitro group (44,52).

This method is described below and represented by the following equation:

$$\underset{\text{CO-C}_2\text{H}_5}{\overset{\text{N}_2\text{BF}_4}{\bigcirc}} + \text{NaNO}_2 \xrightarrow{\text{cu}} \underset{\text{CO-C}_2\text{H}_5}{\overset{\text{NO}_2}{\bigcirc}} + \text{N}_2 + \text{NaBF}_4$$
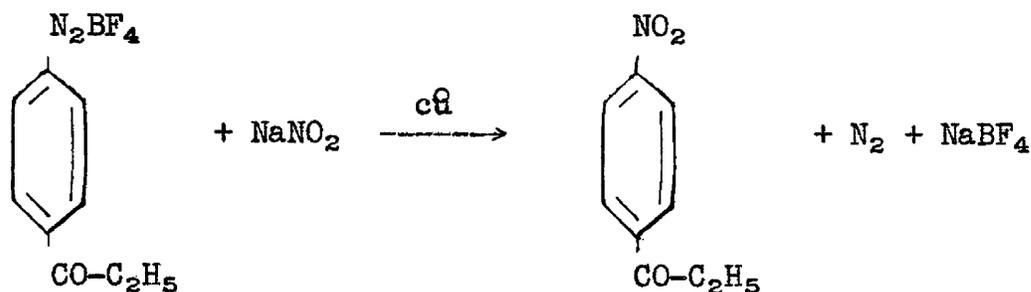
Add 31.1 g. (0.125 mole) of p-propionylphenyldiazonium (preparation previously given) to 10 cc of cold water to make a fine aqueous paste. This paste is slowly added to a rapidly stirred suspension of 20 g. of copper metal, precipitated powder, in a solution of 80 g. of sodium nitrite in 160 cc of water, contained in a one liter beaker. The reaction is carried out at room temperature. The walls of the beaker are washed down from time to time with very small amounts of water. The diazonium borofluoride is added over a period of half an hour; a few cc of ether is used from time to time to control the copious frothing produced by the evolution of nitrogen. A small amount of material is withdrawn now and then to test for the free diazonium compound, which produces a red coloration with a few drops of alcoholic alkaline β -napthol solution. After no more diazonium compound has been detected, the stirring is continued for fifteen minutes. Then the reaction mixture is made alkaline with ten per-cent sodium hydroxide solution and stirred again for 10 minutes. The product is filtered with suction, washed several times with water, twice with dilute sodium hydroxide solution, and again with water. The solid is partially dried by sucking air through it and is then extracted with

50 percent hot alcohol. The resulting yellow crystals, melting at 86–87° C., weigh **4.8** g. (22 percent yield). Recrystallization from hot water and decolorization with norite yields pale yellow crystals m.p. 90–91° C. (cor). Further recrystallization produces no change in melting point.

The above method is generally followed, however, in some runs, benzene is used as the solvent in place of the hot alcohol. The benzene is then extracted with 10 percent sodium hydroxide; the benzene evaporated off on a steam bath and a blackish solid residue remains which is taken up in 50 percent alcohol and heated with charcoal whereby yellow crystals, melting at 87° C. are obtained. These crystals on recrystallization melt at 90–91° C. (cor.).

The p-nitropropiophenone is a yellow crystalline solid, soluble in hot water, alcohol, benzene and ether; insoluble in cold alkali and water; and gives no reaction with ferric chloride solution.

<div align="center">Analysis of p-Nitropropiophenone</div>

Found nitrogen (Kjeldahl)	7.72 % N	7.75% N
Calculated nitrogen for $C_9H_9O_3N$	7.82% N	

<u>Oxidation of p-Nitropropiophenone.</u> One gram of p-nitropropiophenone is added to 80 cc of water containing 4 g. of potassium permanganate; one cc of 10 percent sodium hydroxide solution is added and the mixture heated under reflux until the purple color of the permanganate disappears (4 hours). At the end of this time,the mixture is cooled and carefully acidified with sulfuric acid. The mixture is again heated for one half an hour and then cooled. The excess manganese dioxide is removed by the addition of a little sodium bisulfite

solution. The precipitated acid is collected on a filter and re-crystallized from dilute alcohol; the product melts at 240°C. p-Nitrobenzoic acid is described as melting at 240°-242° C. (Lang's Handbook of Chemistry); meta-141° C.; ortho-147° C. Thus proving that the position of the nitro group is para to the propionyl.

Oxime of p-Nitropropiophenone. This oxime is prepared in the regular manner. After recrystallization from dilute alcohol, forms a white crystalline solid, melting at 124° C.(dec). It is soluble in alkali and in alcohol and insoluble in water.

The three isomeric mononitropropiophenones are now fully charac-terized:- ortho - liquid; meta - crystalline, m.p. 98° C.(cor); para - crystalline, m.p. 90-91° C.(cor).

Confirmation for the p-isomer is seen in the following:

(a) p-Aminopropiophenone, from which the nitro-compound was obtained, has been converted into the known p-hydroxy-derivative.

(b) Analysis shows that it is a mono-nitro compound.

(c) As shown above, the ketone may be oxidized to p-nitro-benzoic acid.

(d) The oxime has been prepared as a characteristic derivative.

p-Propionylphenylarsonic Acid. Of the various methods for pre-paring aromatic arsonic acids, that developed by Bart has been most widely used. Solutions of diazonium chlorides or sulfates are added to sodium arsenite in alkaline or neutral solution in the presence of various metals or their salts.

Ruddy found that the Bart reaction may be conveniently adapted to the use of diazonium borofluoride intermediates (43). Applied to p-aminopropiophenone, this reaction may be represented as follows:

NH$_2$

+ HBF$_4$ + NaNO$_2$ ⟶

N$_2$BF$_4$

+

$$\xrightarrow[\text{Cu}_2\text{Cl}_2]{\text{Na}_2\text{HAsO}_3}$$

CO-C$_2$H$_5$

CO-C$_2$H$_5$

AsO$_3$H$_2$

CO-C$_2$H$_5$
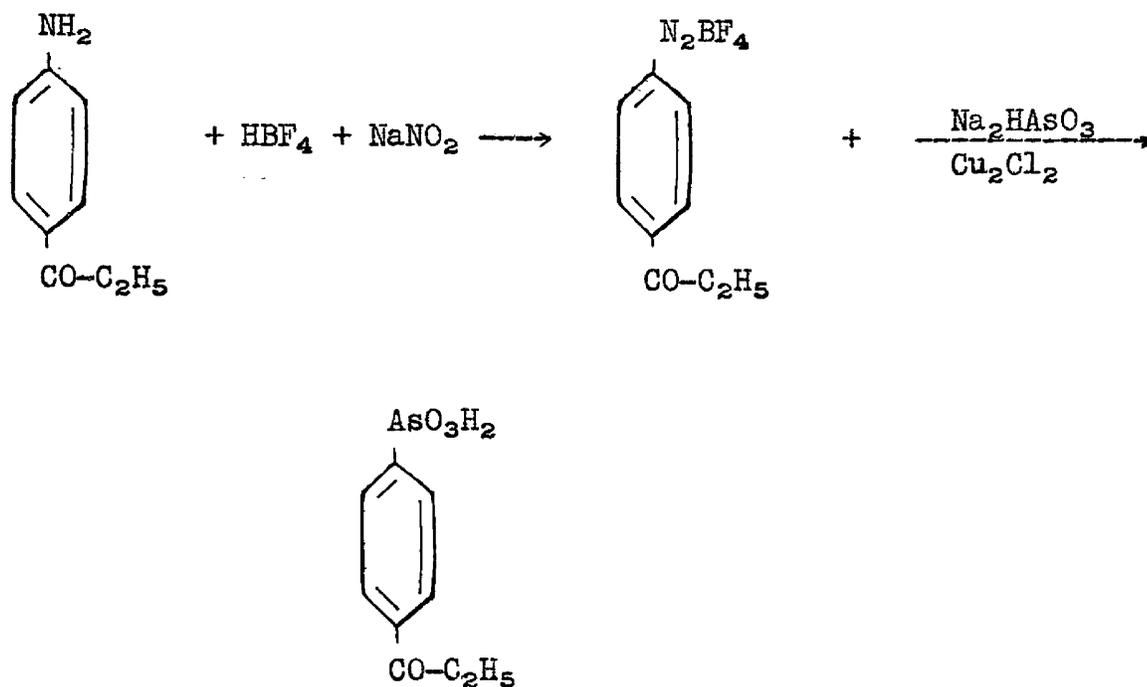
Eighteen grams of p-propionylphenyldiazoniumborofluoride (0.07 mole),

is suspended in 60 cc water and slowly added with vigorous stirring,

over a period of fifteen minutes, to a solution containing 9.1 g.

(0.07 mole) of sodium meta-arsenite (NaAsO$_2$), 27 cc of 10 percent

sodium hydroxide solution (0.07 mole), and 2 g. of cuprous chloride,

in 100 cc of water at room temperature. Ether is used to control

excessive foaming produced by the evolution of nitrogen. Seventeen

cc of 10 percent sodium hydroxide (0.014 mole) is added to maintain

the proper alkalinity. The reaction mixture is then stirred for an

additional 15 minutes and allowed to stand over night at room tem-

perature. It is then heated to 65° C. for half an hour and the by-

products and copper salts filtered out with suction. The filtrate

is acidified to litimus paper with concentrated hydrochloric acid

and any tarry material separating is filtered off. The filtrate is

then concentrated with charcoal to 50 cc, filtered and the hot

filtrate acidified to congo-red paper with concentrated hydrochloric

acid. The solution is cooled and the precipitated p-propiophenylarsonic acid is filtered off. A second crop of crystals is obtained by further concentrating the mother liquor. The combined crops are then recrystallized and decolorized with charcoal from water. The weight of which crystals is 9 g. representing 48-50 percent of the theoretical yield. This arsenical has a decomposition range of $310°$ to $311.5°$ during which period of temperature it changes from a white crystalline solid to a brownish amorphous solid. No analysis of this product was made because of the small amount available.

Isonitroso Compounds

Claisen and Manasse (54) were the first to describe the general nitrosation reaction as applied to ketones of the type $AR-CO-CH_2R$, where R is a methyl or any alkyl group, resulting in the formation of isonitroso compounds. This reaction is indicated by the equation

$$AR-CO-CH_2R \quad \xrightarrow{\quad RONO \quad} \quad AR-CO-CH(:NOH)R.$$
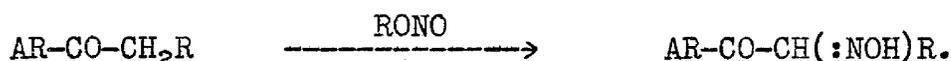
Subsequent studies by Slater (54) and Hartung and his associates (2,9,15,55,56), indicate that the products $AR-CO-CH(:NOH)R$, may be prepared pure and in good yields.

p-Aminoisonitrosopropiophenone. Many attempts were made to nitrosate p-aminopropiophenone but in each instance there resulted such a mixture of products and large proportions of tar that only small amounts of impure crystalline product could be isolated. Insufficient material was isolated to permit analysis. Results discouraged further attempts along this line.

The following is a typical example of an attempt at the nitrosation of p-aminopropiophenone:

In a half liter, three-neck round bottom flask provided with a sealed mechanical stirrer, a reflux condenser connected to a gas absorption trap, a delivery tube for hydrogen chloride, and a small dropping funnel are placed 7.0 g. (0.05 mole) of p-aminopropiophenone in 200 cc of ether. Hydrogen chloride (generated by allowing concentrated sulfuric acid to drop on concentrated hydrochloric acid) is passed through the stirred solution at the rate of 2-3 bubbles per second. However, at the same time, the p-aminopropiophenone precipitates out as the hydrochloride. Stirring and addition of acid are continued throughout the reaction. Then 5.2 g. (0.05 mole) freshly distilled butyl nitrite are added in 0.5 cc portions from the dropping funnel. After addition of the first portion, the reaction mixture becomes brownish and fifteen minutes later, it becomes light brown in color. After the second portion of nitrite, some of the suspended material goes into solution, and a similar color change takes place. A third portion is added and so on until all the nitrite is used. However, at no time are all the materials in solution. The mixture gradually warms up and the ether layer begins to reflux gently. After all the nitrite has been added, taking about 20 minutes, stirring and addition of hydrogen chloride are continued for another fifteen minutes. The reaction mixture is then allowed to stand for one hour. Next the ethereal suspension is slowly stirred into dilute sodium hydroxide containing pieces of ice, and the ethereal suspension is repeatedly extracted with cold alkali

until all of the suspended product goes into solution. Cold acetic
acid is slowly stirred into the alkaline extracts, but no precipitate
appears; then this solution is made alkaline with ten percent sodium
bicarbonate solution and an orange precipitate appears. This is taken
up in ether and forced out with benzene to give an orange colored
crystalline solid, melting at 129-130° C. After recrystallization from
hot fifty percent alcohol, melting at 129-130° C.(cor), these crystals
are soluble in dilute hydrochloric acid or acetic acid producing a
yellow color. They are also soluble in sodium hydroxide, forming a
purple solution.

The experiment was repeated using as the solvent ether saturated
with water. In this instance several products were isolated, one of
which melted at 157-162° C. (dec). When the aqueous extract was made
alkaline, a precipitate was collected melting at 90-95° C. (dec).
The alkaline mother liquors were acidified with concentrated hydro-
chloric acid and a precipitate melting at 157.5-160° C. (dec.) was
obtained. Of all the products isolated, it would seem that the
crystals melting at 129-130° C. may be the p-aminoisonitrosopropio-
phenone; they are soluble in both acid and alkali.

p-Nitroisonitrosopropiophenone.
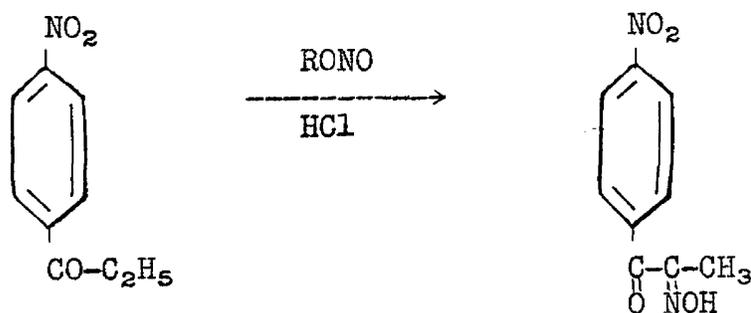
Since this reaction proceeds normally, only one typical example is

given. In a half liter three-neck, round bottom flask provided with a sealed mechanical stirrer, a reflux condenser connected to a gas absorption trap, a delivery tube for hydrogen chloride and a small dropping funnel are dissolved 9.0 g. (0.05 mole) of p-nitropropiophenone in 150 cc of ether. Hydrogen chloride (generated by allowing concentrated sulfuric acid to drop on concentrated hydrochloric acid) is passed through the stirred solution at the rate of 2-3 bubbles per second, stirring and addition of acid are continued throughout the reaction. Then 5.2 g. of freshly distilled butyl nitrite (0.05 mole) is added from the dropping funnel, in 0.5 cc portions. After addition of the first portion, the reaction mixture becomes an orange brown color, and after several minutes, a lighter color; after this second portion of nitrite is added, followed by a similar color change, then a third portion is added, etc. The mixture gradually warms up and the ether begins to reflux gently. After all of the nitrite has been added, taking about 20 minutes, stirring and addition of hydrogen chloride are continued for another fifteen minutes. The reaction mixture is then allowed to stand over night at room temperature. Next the ethereal solution is slowly stirred into dilute sodium hydroxide, containing pieces of ice, and the ethereal suspension is repeatedly extracted with cold alkali until it remains colorless. The combined alkaline extracts are slowly stirred into concentrated hydrochloric acid containing sufficient ice to keep the reaction mixture cold. In this manner 7.0 g. of white crystals are collected. These melt at 129-130° C. and represent a yield of 70 percent. After recrystallization from dilute

alcohol and decolorized with charcoal, they melt at 132-133° C.
Further recrystallization from water produces no further change in
melting point.

Analysis of p-Nitroisonitrosopropiophenone

Found nitrogen (Kjeldahl)   13.35% N   13.32% N

Calculated nitrogen for $C_9H_8O_4N_2$ 13.46% N

Oximation of p-Nitroisonitrosopropiophenone.
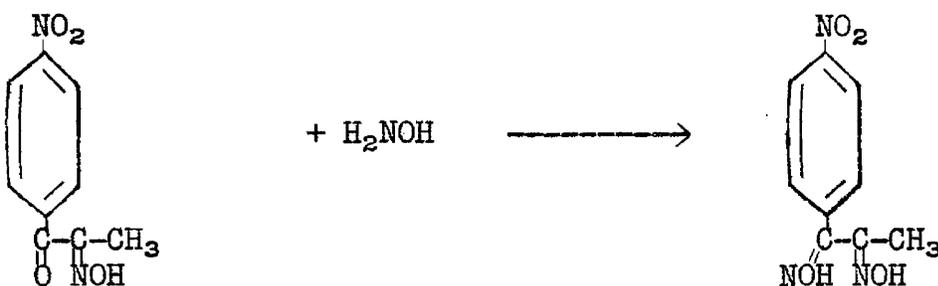
A solution of 0.5 g. of hydroxylamine hydrochloride in 3 cc of water
is added to a solution of 1 g. of the p-nitroisonitrosopropiophenone.
Sufficient alcohol is added, drop by drop, until a clear solution
results. After allowing the reaction mixture to stand for three to
five days, crystals begin to precipitate; after two weeks, the
crystals obtained are filtered, dried and recrystallized from dilute
alcohol. The slightly yellow glyoxime melts at 197-198° C. (dec).
This glyoxime added to an ammoniacal solution of nickelous chloride
produces a bright red precipitate.

p-Acetaminoisonitrosopropiophenone.

NH-CO-CH₃ ... RONO / HCl → NH-CO-CH₃ ... C-C-CH₃ / O NOH

(structural reaction scheme)
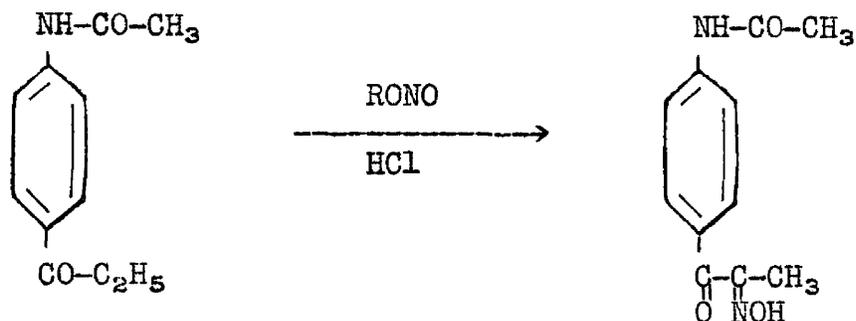
Since this reaction proceeds normally, only one typical example is given. In a 500 cc three-neck, round bottom flask provided with a sealed mechanical stirrer, a reflux condenser connected to a gas absorption trap, a delivery tube for hydrogen chloride and a small dropping funnel is suspended 20 g. of p-acetaminopropiophenone (0.10 mole) in 400 cc of ether. Hydrogen chloride is passed through the stirred solution at the rate of 2-3 bubbles per second, stirring and addition of acid are continued throughout the reaction. Then 13.5 g. of freshly distilled butyl nitrite (0.13 mole) is added from the dropping funnel, in 0.5 cc portions. After addition of the first portion, the reaction mixture becomes a slight orange color and after several minutes, a lighter color; after this a second portion of nitrite is added and a similar color change takes place, whereupon a third portion is added, etc. At no time is solution complete but the crystals undergo a change in color (white to slight yellow) and structure as the reaction proceeds. The mixture gradually warms up and the ether begins to reflux gently. After all of the nitrite has been added, taking about one and a half hours, stirring and addition

of hydrogen chloride are continued for another half an hour; after

which the reaction mixture is allowed to stand over night at room

temperature. Then the ethereal solution is slowly stirred into

dilute sodium hydroxide containing pieces of ice, and the ethereal

suspension is repeatedly extracted with cold alkali until no more

product is obtained. The alkaline extracts are slowly stirred into

concentrated hydrochloric acid containing sufficient ice to keep the

reaction mixture cold. In this manner 17.0 g. of white crystals are

obtained, representing 75% of the theoretical yield. The p-acetamino-

isonitrosopropiophenone melts at 216° C.(cor). After decolorization

with charcoal and recrystallization from 50% alcohol, melts at 218-

219° C.(dec). Further recrystallizations produce no further change

in melting point.

Analysis of p-Acetaminoisonitrosopropiophenone

Found nitrogen (Kjeldahl)	12.69% N	12.75% N
Calculated nitrogen for $C_{11}H_{12}O_3N_2$	12.72% N	

Oximation of p-Acetaminoisonitrosopropiophenone.

NH-CO-CH₃ ... + H₂NOH ⟶ NH-CO-CH₃
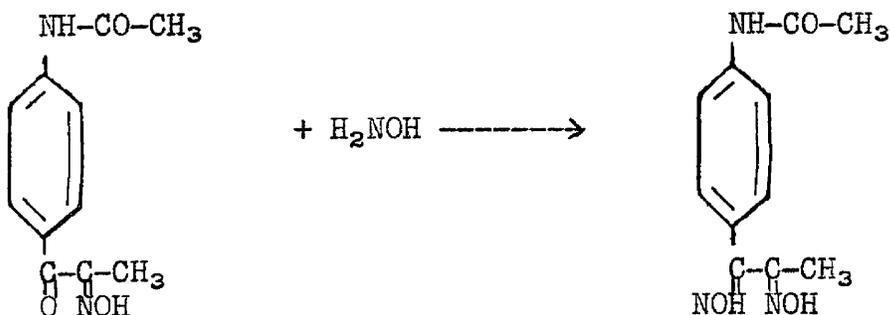
This procedure is identical to that under the "Oximation of p-

Nitroisonitrosopropiophenone".

The glyoxime is a white crystalline solid, recrystallizable from

alcohol, melting at 225-226° C. (dec). This glyoxime when added

to ammoniacal solution of nickelous chloride produces a yellow-

orange precipitate. This yellow-orange precipitate is soluble in

benzene and can be thrown out of the benzene by the addition of

petroleum ether.

p-Benzoylaminoisonitrosopropiophenone.
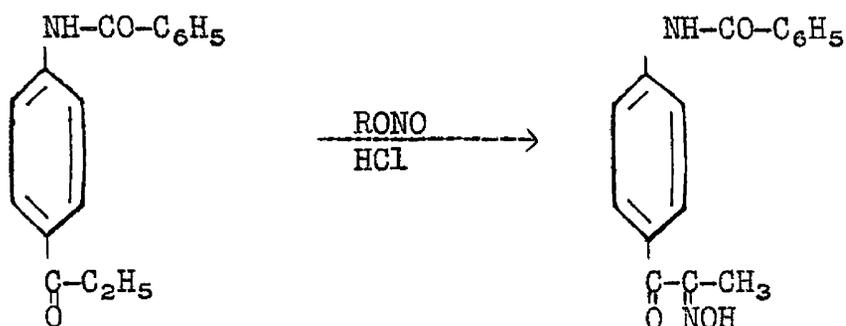
Nitrosation of p-benzoylaminopropiophenone proceeds by the same

method given under p-acetaminopropiophenone.

To a suspension of 10 g. (0.04 mole) p-benzoylaminopropiophenone

in 500 cc ether is added 3.5 cc (0.04 mole) butyl nitrite. Nitro-

sation proceeds as usual. Recrystallization of the crude product

from alcohol gives 8-9 g. of fine white crystals, decomposing at 207° C.

(cor); after recrystallization from alcohol, melts at 209-210° C.(dec).

Further recrystallization produces no further change in the melting

point.

Analysis of p-Benzoylaminoisonitrosopropiophenone

Found nitrogen (Kjeldahl)	9.84% N	9.81% N
Calculated nitrogen for $C_{16}H_{14}O_3N_2$	9.93% N	

Oximation of p-Benzoylaminoisonitrosopropiophenone. This procedure is identical to that given under "Oximation of p-Nitroisonitrosopropiophenone".

The glyoxime is a white crystalline solid, recrystallizable from alcohol, melting at 243-244° C.(dec). This glyoxime added to an ammoniacal solution of nickelous chloride produces an orange precipitate. This is soluble in benzene and may be thrown out of the benzene by the addition of petroleum ether.

The nitrosation of p-acetamino- or p-benzoylamino-propiophenone is not affected if the amount of butyl nitrite or isopropyl nitrite is increased over the theoretical amount. The molecular ratios may be used as follows: One mole of the ketone with one mole of nitrite; one mole of ketone with two moles of nitrite or one mole of ketone with three moles of nitrite. However, it was found that the excess of nitrite did not have any effect on the quality of final product, and often times an excess of the nitrite was added with beneficial effect on the yield if the reaction seemed to warrant it.

p-Isonitrosopropionylphenylarsonic Acid.
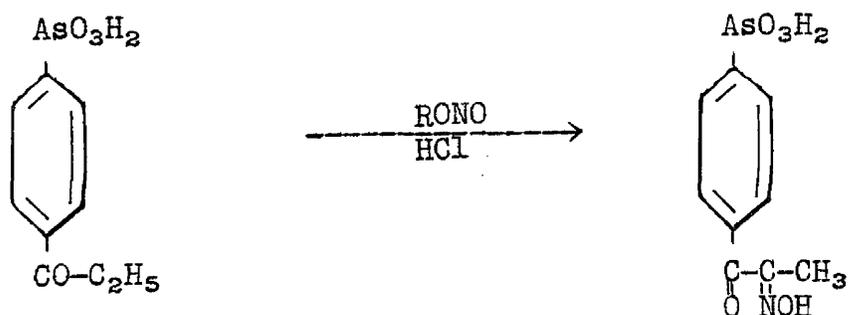
In a 500 cc three-neck, round bottom flask provided with a sealed mechanical stirrer, a reflux condenser connected to a gas absorption

trap, a delivery tube for hydrogen chloride and a small dropping funnel is suspended 6 g. (0.031 mole) in 200 cc ether and 50 cc alcohol are passed through the stirred solution at the rate of 2-3 bubbles per second, stirring and addition of acid are continued throughout the reaction. Then 5.4 g.(0.062 mole) butyl nitrite is added from the dropping funnel in 0.5 cc portions. After addition of the first portion, the reaction mixture becomes a slight orange color and after several minutes, a lighter color; after this second portion of nitrite is added and a similar color change takes place, a third portion is added, etc. The crystals tend to dissolve as the reaction proceeds. The mixture gradually warms up and the ether begins to reflux gently. After all the nitrite has been added, taking about one and a half hours, stirring and addition of hydrogen chloride are continued for another half an hour; the reaction mixture is allowed to stand for one hour at room temperature. The reflux condenser is then inverted, stirring is resumed, and the solvent recovered by distillation under reduced pressure. When all of the solvent is removed, the crude product thus obtained is then decolorized with charcoal and recrystallized from hot water. Four grams of a white crystalline precipitate are obtained, representing a yield of 60 percent. This compound has a decomposition range from 322-325° C. Further recrystallization produces no further change in the decomposition range.

Oximation of p-Isonitrosopropionylphenylarsonic Acid.

AsO_3H_2

$+ H_2NOH \longrightarrow$

AsO_3H_2

C-C-CH₃
O NOH

C-C-CH₃
NOH NOH
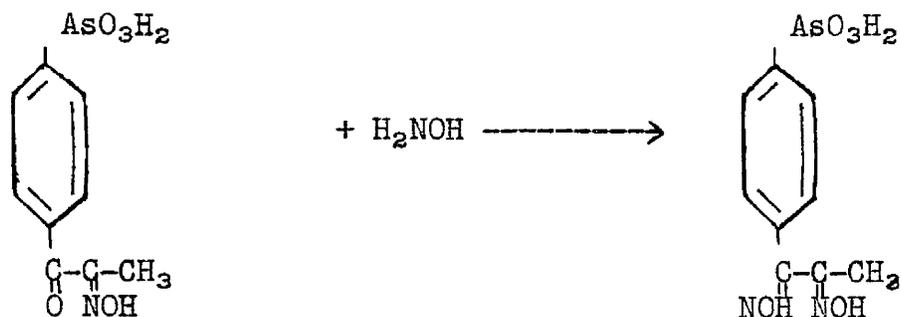
This procedure is identical to that under "Oximation of p-Nitroisonitroso-propiophenone".

The glyoxime is a white crystalline solid, recrystallizable from dilute alcohol, melting at 245-246° C.(dec). This glyoxime added to an ammoniacal solution of nickelous chloride produces a yellow to orange precipitate.

Catalytic Hydrogenation of Isonitrosoketones in the Presence of Palladium.

Catalytic reduction of organic compounds by means of metal catalysts has received the attention of chemists for about the last fifty years. Paul Sabatier (58) was an early leader in this field, he being the first to show that by means of nickel and hydrogen benzene and similar compounds could be converted into the corresponding cyclohexane derivatives.

Studies by Hartung and his associates (2,4,9,15,16) show that isonitrosoketones of the type, AR.CO.C(:NOH)R, where R is any alkyl group, may be reduced using palladium-charcoal catalyst to the corresponding aminoalcohols, AR.CHOH.CHRNH$_2$, in good yields.

$$AR.CO.CHR(:NOH) + 3H_2 \xrightarrow[HCl]{Pd} AR.CHOH.CHRNH_2 + H_2O$$
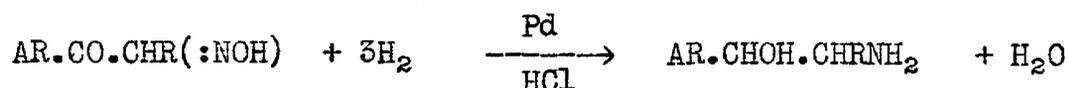
Catalysts. The palladium-charcoal catalysts are prepared by the same method as described by Hartung (59). The general procedure follows: To 100 cc of distilled water is added 0.3 g. of palladium chloride and 3.0 g. of Norite, they are shaken in an atmosphere of hydrogen until saturated. The palladinized-charcoal thus obtained is filtered off, washed with distilled water, followed by alcohol, ether and dried with suction. Drying requires only about five to ten minutes. In some instances, highly active catalysts begin to glow on drying and even ignite; the glow is immediately quenched with water and the catalyst again washed with alcohol and used before all the alcohol has evaporated.

Reduction Mixture. This mixture is prepared by dissolving or suspending the isonitroso-ketone in alcoholic-hydrogen chloride. The palladinized-charcoal catalyst is then added and the suspension shaken in an atmosphere of hydrogen. The apparatus used is either that described by Hartung (59,60,61) or the catalytic hydrogenation apparatus

purchased from the American Instrument Company, which employs hydrogen under pressure.

The alcoholic-hydrogen chloride is prepared by passing dry hydrogen chloride into commercial absolute ethanol. This solution of known concentration is kept in a well-stoppered bottle in the refrigerator and diluted as needed.

Reduction of p-Nitroisonitrosopropiophenone.
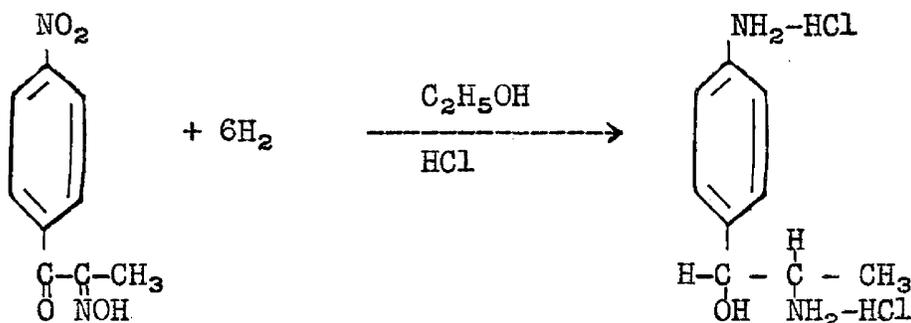
This reduction may be carried out at atmospheric pressure (59) or under pressure. The reduction in the pressure hydrogenation apparatus proceeds as follows: Three grams (0.014 mole) of p-nitro-isonitrosopropiophenone, the previously described palladinized-charcoal catalyst, and 90 cc of alcoholic-hydrogen chloride (2N in HCl) are added to a glass bomb which is the reaction chamber. The reduction proceeds smoothly as shown in Table X.

The product from this reaction is isolated by filtering off the catalyst and evaporating the filtrate to dryness over concentrated sulfuric acid, soda lime and anhydrous calcium chloride in an evacuated desiccator. The pale yellow crystals thus obtained are then dissolved in warm alcohol, charcoal added and filtered slowly into boiling xylene, whereupon a white crystalline product precipitates out. These

Table X.

Reduction of p-Nitroisonitrosopropiophenone

Time	Period- Total Minutes	Readings in Pounds[a]	Pounds of H_2 Consumed	Total cc Consumed	Notes
2.30	–	200	–	–	
2.35	5	195	5	330	
2.40	10	180	20	1330	
2.45	15	176	24	1600	
2.50	20	174	26	1730	Probably has reached ketone stage.
2.55	25	173	27	1800	
3.00	30	173	27	1800	
3.00	50	172	28	1860	
3.50	80	171	29	1930	
4.15	105	171	29	1930	Theoretical amount is 1929 cc
4.30	120	171	29	1930	

[a] A drop of fifteen pounds in pressure is equivalent to 1000 cc.

crystals are washed with ether and dried by suction, decompose at
192-193° C.(cor); two grams are isolated representing a 60 percent
yield. Further recrystallization produces no further change in melt-
ing point. This compound is soluble in water, alkali, alcohol, and
insoluble in ether. It is soluble in ammonium hydroxide without the
production of a color reaction; it does not reduce Fehling's solution;
these negative tests indicate the absence of aminoketone.

Analysis of Dihydrochloride of p-Aminopropadrine

Found chlorine (Volhard)   29.62% Cl   29.60% Cl

Calculated chlorine for $C_9H_{14}ON_2$.2HCl   29.71% Cl

The Reduction of p-Nitroisonitrosopropiophenone at Atmospheric
Pressure.
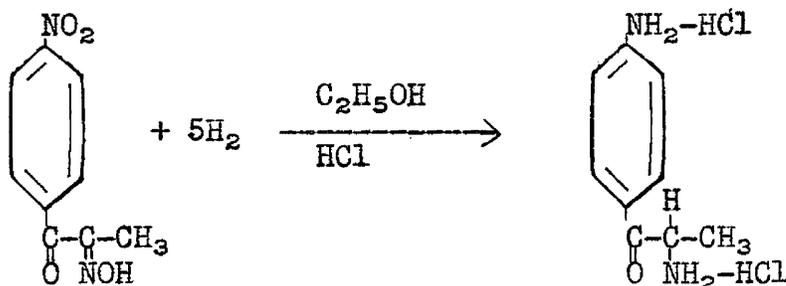
Three grams (0.014 mole) of p-nitroisonitrosopropiophenone, fresh
palladinized-charcoal catalyst previously described, and 90 cc of
alcoholic-hydrogen chloride (2N in HCl) are added to the reaction
flask. The reaction proceeds smoothly at first, and when 5/6ths
of the theoretical quantity of hydrogen is taken up (1607 cc) the
reduction stops. The product is isolated by filtering off the catalyst
and evaporating the filtrate to dryness over concentrated sulfuric
acid, soda lime and anhydrous calcium chloride in an evacuated
desiccator. The pale yellow crystals thus obtained are dissolved in

boiling absolute alcohol, charcoal added and the filtered solution is added to boiling xylene, same as in the previous procedure, but instead of crystals, a gum-like mass is obtained. It is necessary to dissolve this gum-like mass in alcohol, filter, cool and add anhydrous ether, whereupon slight yellow crystals precipitate.

These crystals are soluble in alcohol and water and insoluble in ether. One and a half grams is obtained representing a 44% yield. The compound on heating to 300° C. (cor) gradually darkens but shows no signs of melting. This product reduces Fehling's solution and also reacts with ammonium hydroxide to give yellow crystals which produce a red coloration in an acid medium indicating a pyrazine. This product is undoubtedly the aminoketone, $p-NH_2C_6H_4-CO-CHNH_2-CH_3$.

Analysis of p-Aminophenyl-∝-aminoethyl ketone

Found chlorine (volhard)   29.6% Cl   29.7% Cl

Calculated chlorine for $C_9H_{12}ON_2 \cdot 2HCl$ 30.1% Cl

Reduction of p-Acetaminoisonitrosopropiophenone.
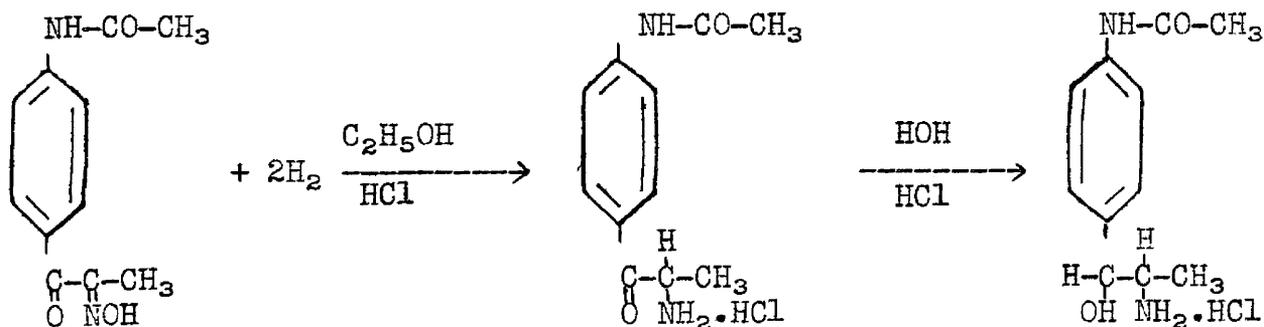
This reduction is carried out in the catalytic-hydrogenation apparatus (A.I.Co.). Suspend 7.0 g. (0.32 mole) of p-acetaminoisonitroso-and a fresh catalyst in 100 cc of alcoholic hydrogen chloride (2N in HCl). Starting out with a pressure of 200 lb. the reaction proceeds smoothly

for about 48 minutes until 2/3rds of the theoretical quantity of
hydrogen is taken up (1400 cc), whereupon the reduction stops. The
product is isolated by filtering off the catalyst and then the char-
coal layer is completely extracted with hot alcohol to put all of the
undissolved reduction product in solution. The combined extracts
are then evaporated to dryness over concentrated sulfuric acid, soda
lime, and anhydrous calcium chloride in an evacuated desiccator.
Seven and half grams of white crystals thus obtained, representing
a 97% yield, are recrystallized from hot alcohol and melt at 257-
258° C. (dec).

p-Acetaminophenyl-α-aminoethyl ketone hydrochloride is soluble
in water and warm alcohol and insoluble in ether. It reacts with
ammonium hydroxide to produce deep yellow colored crystals which are
soluble in dilute hydrochloric acid producing a cherry red coloration
which is characteristic of the pyrazines.

Reduction of p-Acetaminophenyl-α-aminoethyl ketone. The 7.5
g. (0.039 mole) of p-Acetaminophenyl-α-aminoethyl ketone is dissolved
in 10 cc of dilute hydrochloric acid and added to 90 cc of water and
a freshly prepared catalyst. The reduction is started under a 100 lb
pressure and in 30 minutes the ketone takes up the theoretical amount
of hydrogen (680 cc). The product is isolated by filtering off the
catalyst and evaporating the filtrate to dryness over concentrated
sulfuric acid, soda lime and anhydrous calcium chloride in an evacuated
desiccator. The white crystals thus obtained are extracted with cold
anhydrous alcohol, in which only part dissolve and the filtered so-
lution slowly dropped into boiling xylene or toluene, whereby nice white

crystals precipitate. These crystals when washed with ether and dried by suction, weigh 2.0 g. and decompose at 192-193° C. (dec). The melting point agrees with that given by Oberlin (22) for the dihydrochloride of p-aminopropadrine. Analyses further confirm the identity of the compound.

Analysis

Found chlorine (Volhard)	29.54% Cl	29.76% Cl
Calculated chlorine for $C_9H_{14}ON.2HCl$	29.71% Cl	

The white crystals which do not dissolve in the cold alcohol are dissolved in hot alcohol, filtered and then slowly added to boiling xylene or toluene, whereupon white crystals precipitate. These crystals when washed with ether, dried by suction, weigh 1.5 g. and have a melting point of 236-237° C.(dec).

Analysis of these crystals prove them to be p-acetaminopropadrine hydrochloride.

Analysis

Found chlorine (Volhard)	14.77% Cl	14.92% Cl
Calculated for $C_{11}H_{16}O_2N_2.HCl$	14.50% Cl	

Other reductions of p-acetaminoisonitrosopropiophenone were tried and in all cases there was at least partial hydrolysis and in some instances complete hydrolysis.

Hydrolysis of p-Acetaminopropadrine. (a) Half gram of p-acetaminopropadrine hydrochloride is refluxed for one half hour with 20 cc of concentrated hydrochloric acid. The reaction mixture is cooled, filtered and the filtrate evaporated to dryness on a steam bath. The residue is dissolved in alcohol and precipitated with ether. The pre-

cipitate of white crystals melts at 107-108° C.(dec). Chlorine

analysis of these crystals shows 23.4% Cl.

(b) Half gram of p-acetaminopropadrine is refluxed for 1.5 hours

with 30 cc of hydrochloric acid (one part concentrated : one part

water). The reaction mixture is filtered, evaporated nearly to dry-

ness, alcohol added, filtered again and ether added. The precipitate

of yellow crystals is collected, washed with ether and when dry melts

at 162° C.(dec). Chlorine analysis (Volhard) of these crystals shows

26.09% Cl.

These results indicate that p-acetaminopropadrine is not easily

deacetylated. These findings are difficult to reconcile with the

ease with which the acyl-group is removed from p-acylaminopropio-

phenone or as just described, during the catalytic hydrogenation of

p-acetaminophenyl-α-aminoethyl ketone.

Reduction of p-Benzoylaminoisonitrosopropiophenone.
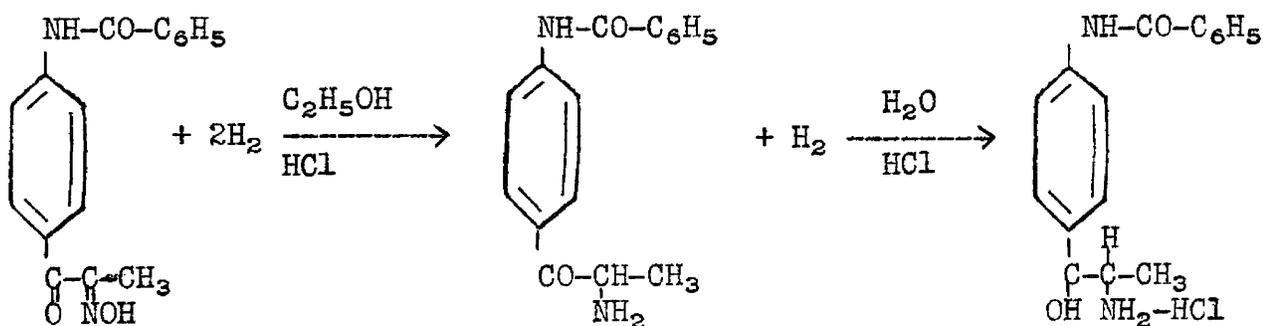
This reduction is carried out in the catalytic hydrogenation apparatus

(A.I.Co.). Suspend 4.0 g. (0.013 mole) of p-benzoylaminoisonitroso-

propiophenone, the palladinized-charcoal catalyst in 100 cc of al-

coholic-hydrogen chloride (2N in HCl). Starting out with a pressure

of 295 lbs. the reaction proceeds smoothly for about 15 minutes until

2/3rds of the calculated amount of hydrogen is taken up (630 cc), where-

upon the reaction stops. The product is isolated by filtering off

the catalyst and completely extracting the charcoal layer with hot

absolute alcohol. The combined extracts are then evaporated nearly

to dryness over concentrated sulfuric acid, soda lime and anhydrous

calcium chloride in an evacuated desiccator. Three and half grams

of white crystals, representing an 81% yield, are recrystallized from

hot alcohol and show no sign of melting when heated up to 340° C.(cor).

These crystals are soluble in water and hot alcohol and insoluble in

ether. They reduce Fehling's solution (on standing over night) and

react with ammonium hydroxide (28%) to produce a yellow precipitate

which is soluble in dilute hydrochloric acid producing a cherry red

coloration, characteristic of the pyrazines. The product is the

hydrochloride of p-benzoylaminophenyl-α-aminoethyl ketone.

Analysis

Found chlorine (Volhard)	11.52% Cl	11.54% Cl
Calculated chlorine for $C_{16}H_{16}O_2N_2 \cdot HCl$	11.65% Cl	

<u>Reduction of p-Benzoylaminophenyl-α-aminoethyl ketone.</u> Three

and a half grams of p-benzoylaminophenyl-α-aminoethyl ketone hydrochloride is dis-

solved in 10 cc of dilute hydrochloric acid and added to 90 cc of

water and a freshly prepared catalyst. The reduction is continued

under pressure of 200 lbs until no more hydrogen is taken up (270 cc),

this requires about 30 minutes. The product is isolated by filtering

off the catalyst and evaporating the filtrate to dryness over con-

centrated sulfuric acid, soda lime and anhydrous calcium chloride in

an evacuated desiccator. The white crystals thus obtained are dis-

solved in absolute alcohol, the solution filtered into boiling xylene, whereupon white crystals precipitate. These crystals when washed with ether and dried weigh 3.0 g., thus representing a yield of 71-72%. These crystals do not melt below 340° C. They neither react with ammonium hydroxide to produce a color reaction nor do they reduce Fehling's solution.

<p align="center">Analysis of p-Benzoylaminopropadrine</p>

Found chlorine (Volhard)	11.49% Cl	11.48% Cl
Calculated for $C_{16}H_{18}O_2N_2 \cdot HCl$	11.58% Cl	

This compound is very soluble in water, soluble in alcohol and insoluble in ether.

The benzoyl-group unlike the acetyl does not hydrolyze spontaneously in any of the reductions. Therefore, various attempts were made to remove this group, but in all of them the desired hydrolysis did not take place.

<u>Hydrolysis of p-Benzoylaminopropadrine.</u> (a) Half gram of p-benzoylaminopropadrine is refluxed for one hour with equal volumes of concentrated hydrochloric acid and water. The products isolated are benzoic acid, unchanged p-benzoylaminopropadrine and some yellow crystals which are not p-aminopropadrine dihydrochloride and are inadequate for further identification.

(b) p-Benzoylaminopropadrine is refluxed for half hour in concentrated hydrochloric acid. The products isolated are benzoic acid, unchanged, p-benzoylaminopropadrine and some yellow crystals, the amount again, insufficient for identification.

(c) Half gram of p-benzoylaminopropadrine is refluxed for one

hour in a solution of 20 cc of concentrated hydrochloric acid and 20 cc of water. The solution is then filtered and evaporated to dryness on a steam bath. The products isolated are benzoic acid, p-benzoylaminopropadrine and some yellow crystals soluble in alcohol and when ether is added, precipitate as a gum-like substance. This gum-like substance is again dissolved in alcohol and slowly filtered into boiling toluene, whereupon a yellow lumpy mass is obtained. This lumpy mass cannot be further purified for analysis.

(d) p-Benzoylaminopropadrine is refluxed for 2 hours in concentrated hydrochloric acid. When allowed to cool, crystals of benzoic acid separate out. The filtrate is evaporated to dryness in a desiccator and yellow crystals, melting at 178-180° C.(cor) are obtained. These crystals are washed with cold acetone and when dry, melt at 178-180° C.; they cannot be identified for the yield is surprisingly low when compared to the amount of benzoic acid obtained.

(e) p-Benzoylaminopropadrine is refluxed with 25 cc of sodium bicarbonate solution (10%), and 10 cc of alcohol for one hour. On cooling the precipitate is collected, dissolved in ether, dry hydrogen chloride added and white crystals of p-benzoylaminopropadrine are obtained.

These attempts at hydrolysis recall the experiments of Abel (62,63) who following his work on the monobenzoyl derivative of epinephrine, makes the following statement:

> I was soon able to demonstrate that my epinephrine had
> retained a single benzoyl radical that had resisted
> saponification and could only be removed from the base
> by drastic treatment with strong acids and heat, a
> treatment which at the same time obliterated every trace
> of the characteristic physiological action of the hormone.

It is not unlikely that such similar compounds as p-benzoyl-aminopropadrine and benzoylepinephrine may be hydrolyzed and benzoic acid isolated, however, the drastic treatments necessary destroy the physiologically active portion of the molecule.

Reduction of p-Isonitrosopropionylphenylarsonic Acid.

$$AsO_3H_2 \quad + 3H_2 \quad \xrightarrow[\text{HCl}]{C_2H_5OH} \quad AsO_3H_2$$
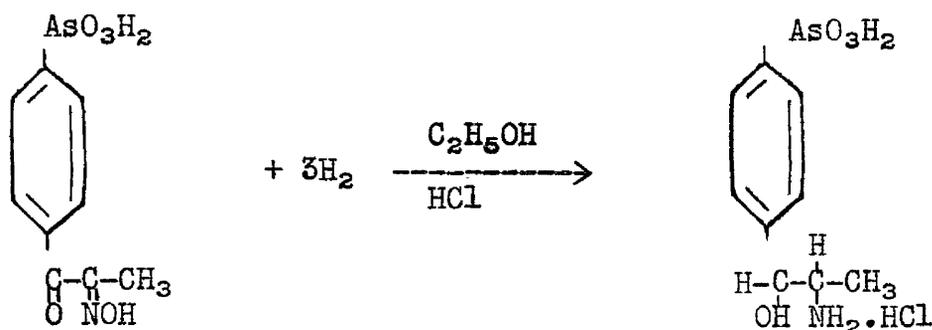
The reduction is carried out in the catalytic hydrogenation apparatus (A.I.Co.) as follows: Dissolve 3.0 g. (0.01 mole) of p-isonitroso-propionylphenylarsonic acid in 30 cc of alcoholic-hydrogen chloride (2N in HCl) and add to the suspended palladinized charcoal catalyst 70 cc of absolute alcohol. The reduction proceeds smoothly as shown in Table XI. The product from this reaction is isolated by warming the reaction mixture, filtering off the catalyst, evaporating the filtrate to dryness over concentrated sulfuric acid, soda lime and anhydrous calcium chloride in an evacuated desiccator. The crystals obtained are then decolorized with charcoal and recrystallized from hot water, melting at 188-189° C.(dec). Further recrystallization produces no further change in the melting point. One and half grams of product is isolated, representing a 50-51% yield. These crystals are insoluble in alcohol, soluble in hot water and give neither a color reaction with ammonium hydroxide (28%) nor reduce Fehling's solution.

Table XI.

Reduction of p-Isonitrosopropionylphenylarsonic Acid

Time	Period-Total Minutes	Readings in Pounds[a]	Pounds of H_2 Consumed	Total cc Consumed	Notes
11.35	–	175.0	–	–	
11.40	5	172.0	3.0	200	
11.45	10	170.0	5.0	330	
11.50	15	169.0	6.0	400	
11.55	20	168.0	7.0	475	
12.00	25	167.5	7.5	500	
1.00	85	164.5	10.5	700	Theoretical amount is 702 cc.
1.10	95	164.5	10.5	700	
2.00	145	164.5	10.5	700	

[a] A drop of fifteen pounds in pressure is equivalent to 1000 cc.

Analysis of p-Arsonopropadrine Hydrochloride

Found chlorine (Volhard   11.70% Cl   11.69% Cl

Calculated for $C_9H_{14}O_2NClAs$ 11.30% Cl

SUMMARY AND CONCLUSIONS

(1) A method has been developed for the synthesis of p-aminopropio-phenone in yields of 30-35 percent. The corresponding diazonium compound has been prepared and upon warming in solution, the p-hydroxypropiophenone was obtained. This confirms the position of the amino group.

(2) The following derivatives have been made and characterized: Hydrochloride, oxime, N-acetyl- , N-benzoyl- , oxime of N-acetyl, oxime of N-benzoyl, diazonium chloride, and diazonium boro-fluoride.

(3) The literature on p-nitropropiophenone was reviewed. This compound is now, so far as known, adequately described for the first time and the correctness of its structure is seen in the following:

    (a) Derivation from p-aminopropiophenone by replacing the amino-group by the nitro-group.

    (b) Oxidation of p-nitropropiophenone to p-nitrobenzoic acid.

    (c) Analysis confirms the presence of a single nitro-group.

    (d) The oxime has been prepared as a characteristic derivative.

(4) The following arsono- compounds have been prepared and characterized: p-Propionylphenylarsonic acid and its oxime.

(5) Extension of the general nitrosation reaction to these aryl-
ketones has been studied; the reaction has been used to pre-
pare the following: p-Nitroisonitrosopropiophenone,
p-acetaminoisonitrosopropiophenone, p-benzoylaminoisonitroso-
propiophenone, p-isonitrosopropionylphenylarsonic acid.

(6) The following nuclear substituted phenylmethyl- glyoximes
were prepared and characterized: p-Nitro, p-acetylamino- ,
p-benzoylamino- , p-arsono- .

(7) The above mentioned glyoximes gave characteristic precipitates
with ammonical nickelous chloride solution.

(8) The isonitroso- compounds numberated above have been subjected
to catalytic hydrogenation. Generally the aminoketone was
first isolated, characterized and further reduced to the
aminoalcohol. The following reductions were carried out:

   (a) p-Nitroisonitrosopropiophenone → p-aminophenyl-
       α-aminoethyl ketone → p-aminopropadrine.

   (b) p-Acetaminoisonitrosopropiophenone → p-acetamino-
       phenyl-α-aminoethyl ketone → p-acetaminopropadrine
       and p-aminopropadrine.

   (c) p-Benzoylaminoisonitrosopropiophenone → p-benzoyl-
       aminophenyl-α-aminoethyl ketone → p-benzoylamino-
       propadrine.

   (d) p-Isonitrosopropionylphenylarsonic acid → p-arsono-
       phenyl-1-amino-2-propanol-1

(9) It has been found that the p-acetyl- and p-benzoyl-propadrine
were not deacetylated. These results are in harmony with the

work of Abel on the hydrolysis of his monobenzoyl derivative of
epinephrine. It is not unlikely that such similar compounds as p-
benzoylaminopropadrine and benzoylepinephrine may be hydrolyzed
and benzoic acid isolated, however, the drastic treatments necessary
destroy the physiologically active portion of the molecule.

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