HALOGEN RING SUBSTITUTED PROPADRINES

BY

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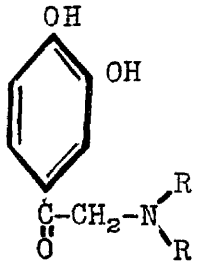
INTRODUCTION

In the constant attempts by the medicinal chemist to increase the efficacy of our ever expanding armamentarium of organic medicinal agents, the correlation between structure and physiological activity is assuming an ever increasing importance. Thus, in the various groups of drugs such as the sulphanilamide derivatives, the barbiturates, the arsenicals, etc. have such studies resulted in the development of new and superior compounds.

To date, perhaps in no field is it possible to correlate better the effect of chemical structure and physiological activity than in the case of the pressor amines. Immediate interest in these compounds was stimulated by the synthesis of epinephrine by Stolz in 1904 (1), with the result that a large number of related compounds have been synthesized and their physiological properties studied. Loewi and Meyer (2) working with a series of ketones of the general formula (I) and the related secondary alcohols (II), including epinephrine (III), found that the reduction of the ketone to the alcohol greatly intensified the epinephrine-like action, which is possessed in some degree by most of these amines. These results were confirmed by Dakin (3) in a similar series. Since all the bases which he examined were catechol derivatives, he was led to the conclusion that it was the catechol nucleus in epinephrine which was the group responsible



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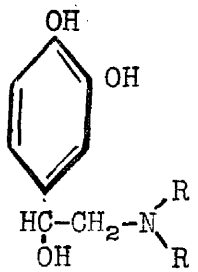

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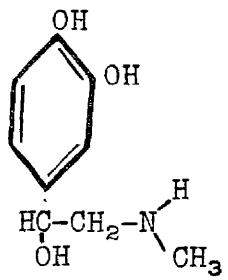

(III)

for its activity. A further basis of this view was the observation that catechol itself on intravenous injection raised blood pressure, while N-methylaminoethanol (the detached side chain of epinephrine) was without such effect. Barger and Dale, having previously noticed that certain amines which were produced by putrefaction and which did not contain a catechol nucleus also had an epinephrine-like action, considered this concept inadequate. Thus, they initiated an investigation upon a series of amines intermediate between the putrefactive amines, in particular p-hydroxy phenylethylamine, and epinephrine itself. This work resulted in their classical paper (4) which appeared in 1910 and which will be referred to in the following discussion.

Dating from this report, a vast amount of pharmacologic data have been accumulated with the result that at present a number of well defined generalizations may be made concerning the effects produced upon the physiological properties of the pressor amines by various alterations in their structure.

REVIEW OF THE RELATIONSHIP BETWEEN CHEMICAL STRUCTURE AND PHYSIOLOGICAL ACTIVITY OF THE SYMPATHOMIMETIC AMINES

I. Sympathomimicity and Pharmacodynamic Classification of the Sympathomimetic Amines

Barger and Dale (4) proposed to call the pressor amines which they has studied, and which simulate the effects of sympathetic nerve stimulation with varying intensity and precision, "sympathomimetic." Although this term was wider and more descriptive than the previously used "adrenine-like," and seemed to indicate the type of action common to these bases, it did not involve any theoretical preconception as to the type of relationship to sympathetic action or to the precise mechanism of action. Moreover, these investigators also recognized the fact that pressor activity, though a convenient index of sympathomimetic action, is not in itself adequate classification. At least some of the other sympathetic nerve effects must be observed before a drug can be classified properly as sympathomimetic. They considered that the association of a pressor action, due to arterial constriction and cardiac acceleration, together with inhibition of the tone and rhythm of the isolated nonpregnant cat uterus as sufficient evidence of sympathomimetic action. These two criteria were used as a basis of their classification.

Although the term sympathomimetic is still frequently applied to these compounds as a class, no special significance should be attached to this term with reference to the mechanism of pressor action, since Tainter and his associates (5,8,15,17,20) have shown that a large number of the pressor amines, especially those which do not contain the catechol nucleus, do not produce their effects by pure sympathetic stimulation. Therefore, the

phrase "sympathomimetic drug" more properly indicates a compound whose action mimics the result of sympathetic nerve stimulation without necessarily acting upon sympathetic innervations. It is thus apparent that a better classification would be one based upon more accurate information concerning the mechanism of action of the pressor drugs. Such an improved classification has been used by Tainter (15) and is based on the results obtained by pharmacodynamic analysis, using the complimentary procedure of ergotaminization and cocainization. These procedures were developed by Tainter as a result of observations which he and other investigators had made.

Dale (45) discovered that ergot paralyzes the sympathetic motor nerves and reverses the pressor action of epinephrine to depressor. Van Dyke (14) as the result of experiments performed on the change of the volume of the nasal cavity produced by sympathetic stimulation before and after ergotoxine supports Dale's view (13) that the epinephrine reversal is due to unparalyzed vasodilator nerves.

Tainter and Chang (5) first observed that otherwise ineffective doses of cocaine prevent the blood pressure rise of tyramine in rabbits, cats, and dogs, while it increases the rise produced by epinephrine, the latter observation having first been made by Froelich and Loewi (6). This immediately suggested a difference in the mechanism by which these two drugs produce their pressor effects. Tainter (7) found that this cocaine sensitization-desensitization phenomenon appeared to be specific for cocaine since it did not occur with other local anesthetics.[1]

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[1]Procaine has also been stated to sensitize the pressor activity of epinephrine (47). Moller (46) found that although procaine produced a small augmentation of pressor effect in intact rabbits, it has no such effect in the perfused isolated rabbit ear. From this he concluded that the effect of procaine is not peripheral and produces its sensitization of epinephrine in intact animals by inhibiting the vasomotor reflexes originating in the carotid sinus.

Subsequently he found that phenylethanolamine (8), ephedrine (9), and synephrine (10), as well as a number of other amines (15) are all similar to tyramine with respect to their behavior in cocainized animals, whereas compounds which contain the catechol nucleus (7,11,12) behave like epinephrine in that their pressor responses are increased by cocaine. Furthermore, cocaine administered subcutaneously to rabbits increases the hyperglycemic effect of epinephrine (7,48) but does not sensitize the responses of the tyramine-ephedrine group (7). Thus cocaine produces its effect even in functions not involving smooth muscle responses.

This difference in the effect of cocaine upon the pressor action of epinephrine and on that of pressors like tyramine suggested its possible use in analyzing drug action, i.e., in determining whether or not the drug acted similarly to epinephrine (true sympathetic stimulant) as indicated by an analogous or different effect of cocaine on their actions. Because of this possible importance of the cocaine phenomenon, a number of studies concerning its mechanism have been carried out and the following facts have afforded several clues to the problem.

(a) The cocaine phenomenon, at least in part, is peripheral and not dependent on the central nervous system; this is indicated by the following results: Tainter (9) was able to demonstrate the cocaine sensitization-desensitization in decerebrated and pithed cats, in cats under different types of anesthesia regardless of the form of anesthesia, as well as in the absence of anesthetics. Further evidence is its demonstration in certain isolated organs and tissues. Thus cocaine increases the action of epinephrine and diminishes or abolishes that of tyramine and ephedrine on the heart (heart lung preparation) of the dog and on perfused blood vessels of the hind limbs (49). Moller (46) has shown that low concentrations of cocaine

which do not alone produce vasoconstriction in the perfused isolated rabbit ear, augment the constrictor effect of epinephrine by 50 to 300%. Additionally, electrocardiographic studies (50) on anesthetized dogs showed that the small doses of cocaine required to produce its effect in modifying pressor actions produce no significant alterations in the conduction system or muscle of the heart; this therefore relegates its site of action to more peripheral structures.

(b) Removal of the adrenals from cats does not decrease cocaine sensitization (46). Therefore, the suprarenals have no bearing on this sensitization.

(c) Studies with several oxidative enzyme systems showed that cocaine does not alter pressor responses by interfering with the oxidative processes of the sympathetic endings or of smooth muscle (7).

(d) Since it is known that the degree of pressor response to epinephrine is altered by pH changes of the blood, this factor was considered. Tainter (12) using cats, was able to show that the pH of the blood did not change after cocainization, and hence pH changes are not the basis of altered pressor responses caused by cocaine.

(e) It was observed that section and degeneration of sympathetic nerves to the iris, heart, blood vessels, etc. result in sensitization to epinephrine. Hence, cocaine, if it blocked the sympathetic endings, might account, on a similar basis, for the sensitized responses of epinephrine. In studying this possibility, Tainter (12), found that the pressor responses elicited by electrical stimulation of splanchnic nerves in adrenalectomized cats is not diminished by cocaine, thus indicating that cocaine does not block the splanchnic nerves.

(f) Cocaine does not augment epinephrine responses by stimulating the central nervous system since Burn and Tainter (49) have demonstrated

that it does not inhibit isolated intestine and virgin cat uterus, does not stimulate isolated auricles, and has a dilator action on blood vessels.

(g) Swanson (51) postulated that cocaine acts on muscle since he found that it abolishes the bronchoconstrictor action of morphine and diethylmorphine, which stimulate bronchial muscle. However Tainter (7) found that papaverine, a muscle depressant, does not alter the pressor responses of epinephrine and tyramine. Thus smooth muscle depression per se can not be advanced as an explanation of cocaine action.

(h) The possibility that cocaine paralyzes vasodilators and hence increases epinephrine responses has also been investigated (12). Sensitization in excised tissues, particularly the heart, where vasodilators can scarcely play a part argues against such a mechanism. Moreover, after cocaine sensitization has been produced in the intact animal, ergotamine still causes a typical epinephrine reversal in the same animal, indicating that the vasodilators are still functioning. In addition, the depressor action of 3,4 dihydroxy-homoethylnorepinephrine (15) also furnishes evidence that the activity of the vasodilators is not altered by cocaine, nor by ergotamine, since these two drugs do not modify the depressor action of that amine.

(i) Burn and Tainter (49) observed that denervation of the pupil of the cat eye sensitizes it to epinephrine while abolishing the effect of tyramine. From this they suggested that epinephrine acts, in part at least, by stimulating the myoneural junction, whereas tyramine acts on sympathetic nerve endings which are destroyed by denervation; therefore cocaine probably increases epinephrine action by altering the myroneural junctions, and decreases tyramine action by depressing

sympathetic endings so that they are less easily stimulated but their conductivity is not decreased.

Though no completely satisfactory explanation of the cocaine phenomenon has yet been advanced, the cocainized animal together with the ergotaminized animal has afforded a practical pharmacological method which Tainter and his associates, as previously stated, have used to classify the sympathomimetic amines.

In the cocainization procedure (15) control pressor responses to the amine in question together with the appropriate dose of epinephrine which produces about a 30 mm. rise in blood pressure are obtained in urethanized cats. Cocaine in doses of 15mg./Kg. is then injected subcutaneously. After allowing 15 minutes for absorption, the control dose of epinephrine is reinjected. A doubling of the epinephrine response indicates adequate cocainization and a normal responding cat. The control dose of the amine in question is reinjected and the response compared with the control response of the same amine. If the response of the amine has been sensitized (increased) it acts like epinephrine; if the response is decreased, it acts differently from epinephrine.

In the ergotaminization procedure (15) control responses to epinephrine and the amine are similarly obtained. Then ergotamine is injected intravenously in doses of 1 mg. at a time until the rise of blood pressure produced by the control dose of epinephrine is reversed to a fall, indicating adequate ergotaminization. The amine is then reinjected and its response compared with the control. If its response is reversed the amine acts like epinephrine.

With these two complimentary procedures, Tainter has subdivided the sympathomimetic compounds which he has studied into three groups.

(a) Sympathicotropic. Those compounds which act like epinephrine by

stimulating sympathetic innervations. The pressor actions of these drugs, like those of epinephrine, are sensitized by cocaine and reversed by ergotamine.

(b) Musculotropic. Those compounds which like barium and pitressin stimulate muscle directly. Since the pressor responses of barium and pitressin are not altered by cocaine and ergotamine, those drugs whose pressor responses are also not altered must act like barium and pitressin and accordingly are also musculotropic.

(c) Pseudo-sympathicotropic. Those compounds whose action is indefinite or intermediate between the other two and which do not completely satisfy the criteria which establish the first two groups. In this group are found a large number of compounds such as ephedrine, phenylpropanolamine, and tyramine whose pressor mechanisms probably do not strictly conform to a single seat of action and concerning whose mechanism of action there is still controversy. It is also conceivable that as our knowledge of these compounds increases, it may be possible to split this group into several subgroups with more clearly defined modes of action.

Tainter (17) has recognized the limitations of this classification in his statement that a more complete classification, based on considerations of the actions in both cocainized and ergotaminized organisms, will ultimately be needed. The simple classification presented above does not suffice to catalogue the graduations and combinations of pressor responses on record. Until further studies and data are available, speculation on the details of the mechanism of action would be premature.

More recently Mulinos and Osborne (52) have questioned the accuracy of Tainter's method of determining the site of action on the basis that he employed intact animals in which reflex and brain stimulations are not easily

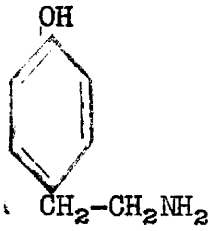
separated from drugs acting peripherally. They asserted that drugs which act on sympathetic ganglia and which stimulate the central nervous system directly or reflexly may appear to be sympathomimetic in the intact animal. In addition the blood pressure rise following stimulation of the C.N.S. maybe reversed by ergot and augmented by cocaine. For example, the reversal of the pressor action of chloracetylcatechol by ergot and its augmentation by cocaine would lead to the conclusion, on the basis of Tainter's method, that this drug acts like epinephrine and is sympathicotropic. However, their experiments indicated that it raises blood pressure by stimulation of the medulla and its action is increased by cocaine only if the medulla is intact. Therefore, in order for the criteria of ergotamine reversal and cocaine synergism to be applicable for analysis of sympathomimetic activity, these investigators maintain that the experiments should be performed on pithed animals. They concluded that in intact animals, ergotamine reversal and cocaine synergism indicates only that impluses eliciting the blood pressure rise reach the blood vessels by way of sympathetic nerves, but do not indicate the site of origin of these impluses.

Burn and Tainter (49) have found that cocaine can depress as well as augment epinephrine action in the same tissue (isolated heart) depending on how the cocaine is supplied to the heart. This brings up the question as to whether it can be concluded that a substance whose action is depressed by cocaine therefore does not act on some part of peripheral sympathetic mechanism.

II. Optimum Skeleton for Activity

If the structures of the better known naturally occurring pressors such as tyramine (IV), epinephrine (III), ephedrine (V) and β-phenyl-ethyl

amine (VI) are examined, it is readily apparent that all possess a structural feature in common; namely, that a phenyl group is attached to a



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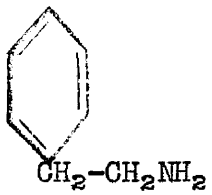


(VI)

terminal carbon and an amino or substituted amino group to the adjacent carbon of an aliphatic chain. Whether or not such an arrangement provides maximum activity has been the object of several investigations.

In considering first the aliphatic amines, Barger and Dale (4) in a study of a series of twenty-one obtained the following results in cats.

(a) The normal chain compounds are more active than the branched or iso chain compounds. Thus isobutylamine was found to be inactive on blood pressure in the doses used, and isoamylamine is less active than n-amylamine but more active than isobutylamine.

(b) Pressor activity begins with n-butylamine and increases with the length of the chain up to six carbon atoms, n-hexylamine being the most active. As the chain is increased from six carbon atoms, the activity decreases while toxicity increases and makes the study of the higher members difficult due to their depressant heart action. Tainter (15) however found that the n-amylamine is the most active of the aliphatic amines.

(c) Primary amines are more active than the corresponding secondary and tertiary amines. Thus methylisoamylamine is only one half as active as isoamylamine.

(d) Introduction of an additional amino group into n-amylamine to form cadaverine $NH_2CH_2-C_3H_6-CH_2NH_2$ reverses the pressor action and converts it to a depressor one.

The activity of the aliphatic amines in general is best summarized by Tainter's statement (15) that their pressor activity is lacking for the majority of these compounds or is weak, variable and unimportant.

Studies of the aromatic portion of the natural pressors have also shown that the aromatic group alone does not represent maximum activity. Although catechol itself does have some pressor activity according to Dakin (3), and Barger and Dale (4), the latter concluded that it had none of the other characteristics of sympathomimetic action. Tainter (11) in analyzing its pressor action found it to be variable and complex and complicated by several side effects which make its blood pressor responses difficult to interpret. In his review of the sympathetic compounds, Hartung (18) states that except for catechol, the aromatic nucleus in itself is not sufficient to produce the desired physiological effect although its presence in these compounds is very important.

That the presence of an amino group is essential for optimum activity is indicated by the study of several compounds lacking this group. Tainter has shown that phenylacetate has no pressor activity (15) while p-ethylphenol shows only an irregular pressor action in cats with the first injection and depression with a second one (17).

The relative position of the amino group in relation to the aromatic nucleus which produces the most active compounds was established by the studies summarized in tables 1 and 2. Barger and Dale (4) from their results (table 1) concluded that "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."

TABLE 1

Optimum Position of the Amino Group (4)

Amine	Pressor Action
1. $C_6H_5NH_2$	None
2. $C_6H_5CH_2NH_2$	Trace
3. $C_6H_5CHNH_2-CH_3$	Trace
4. $C_6H_5CH_2-CH_2NH_2$	Most active of the group. More active than the most active aliphatic amine.
5. $C_6H_5CH_2-CH_2-CH_2NH_2$	Less active than 4.

Hartung and Munch (21) as well as Tainter (15) studied the pressor effects of β-phenylethylamine and a series of four isomeric phenylpropylamines. Their results summarized in table 2 show convincingly that the optimum activity is obtained when the aryl and amino groups are separated by two aliphatic carbons. If the amino group is moved farther from or closer to the phenyl group the degree of activity is diminished. Thus any further increase in activity must result from the introduction of various substituent groups into the molecule. Tainter disagrees with Hartung and Munch as to the pressor value of compound 5 (table 2). Having found this amine to be a poor pressor, Tainter adds an additional condition for optimum activity—the phenyl group must be on a terminal carbon.

Additional evidence to substantiate the above findings is furnished

TABLE 2

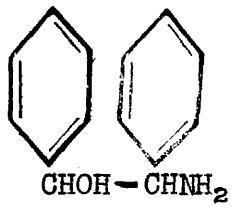
Optimum Position of the Amino Group

Amine	Toxicity-Hydrochloride(21) M.L.D. mg./Kg.		Pressor Activity Dogs-intraven. (21)	Times weaker than epinephrine	Duration pressor rise min.(15)
	Rats subcut.	Rabbits intraven.		Cats(15) intraven.	
1. $C_6H_5 \cdot CH_2 \cdot CH_2NH_2$	450	60	good rise	183	10
2. $C_6H_5 \cdot CHNH_2 \cdot CH_2 \cdot CH_3$	1000	50	slight rise	800	7
3. $C_6H_5 \cdot CH_2 \cdot CHNH_2 \cdot CH_3$	25	25	rise equal and duration greater than 1.	425	17
4. $C_6H_5 \cdot CH_2 \cdot CH_2 \cdot CH_2NH_2$	100	50	medium transitory rise	1471	11
5. $C_6H_5 \cdot CHCH_3 \cdot CH_2NH_2$	500	50	good pressor	1051	5

by the observation of Baehr and Pick (22), Hasama (23) and Tainter (7). The former observed that if in hordenine (VII) the diethylamino group is removed from the aromatic portion by three or four carbon atoms, the pressor potency becomes less. Hasama in comparing the two isomeric phenylethanolamines, $C_6H_5CHNH_2 \cdot CH_2OH$ and $C_6H_5CHOH \cdot CH_2NH_2$, found the first to have no influence on the blood pressure whereas the activity of the second is well established (4,8,24). Tainter observed that if the chain separating the aromatic nucleus in 3,4-dihydroxyphenylethylamine (VIII) is increased to three carbon atoms to produce 3,4-dihydroxyphenylpropylamine (IX), the pressor activity is diminished by two-thirds.

The introduction of an additional phenyl group produces a deleterious

effect on pressor activity. Thus 1,2-diphenylethanolamine (X) is purely depressant on blood pressure as well as on other circulatory functions (23), and bis-(2-phenylethyl)-amine (XI) also produces a fall of blood pressure (7).



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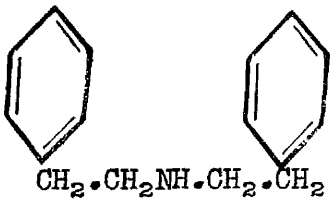


(XI)

III. Effect of Increasing the Length of the Side Chain

A. Increase to three carbon atoms.

By comparing related compounds containing two and three carbon atoms in the aliphatic side chain (table 3) several conclusions may be drawn. The ability to produce a rise in blood pressure is still resident in compounds with a three membered side chain. However, the introduction of a third carbon into a two carbon side chain, in general, decreases the pressor activity, has a variable effect on toxicity and confers oral activity. The propane derivatives produce an effect of longer duration and usually exhibit tachyphylaxis, i.e. successive doses show decreased pressor effects. Another important difference between the ethane and propane derivatives is the ability of the latter to potentiate the pressor response of epinephrine. Launoy and Nicolle (28) observed that the action of epinephrine was increased after ephedrine. The same phenomenon was also observed by Munch and Hartung (29) who reported that the ability to potentiate the pressor action of epinephrine in dogs is characteristic of phenylpropanolamine

derivatives. When the side chain is increased or decreased from a three membered one, the compound no longer shows this potentiation effect.

B. Increase beyond three carbon atoms.

The lengthening of the side chain beyond propyl is attended by a decrease in activity, conversion to a depressor action, and an increase in toxicity (table 4). Chen, Wu and Henriksen (32) found that in perfusion experiments on the frog heart, the increase in the number of carbons increased the depressant heart action. Moreover, toxicity in rabbits (intraven.) ran parallel with the depressant action on the heart. They therefore attribute the lack of pressor action of compounds with long side chains to their depressant action on the heart. For these reasons, the most valuable members of the sympathomimetic amines are those containing side chains of two or three carbon atoms.

IV. Oral Activity and Enzymatic Inactivation

A striking difference between the sympathomimetic amines containing two carbon atoms in the side chain and those containing three is the ability of the latter to show their pressor effects after oral administration, a property lacking in the former.

Chen, Wu and Henriksen (32) attributed the oral efficicacy and prolongation of the activity of ephedrine (V) and propadrin (XII) to the presence of the third carbon in their side chains since they found that phenylethylamine (VI) and phenylethanolamine (XIII)

$CHOH.CHNH_2.CH_3$

(XII)

$CHOH.CH_2NH_2$

(XIII)

Table 3

Comparison of two and three membered side chains

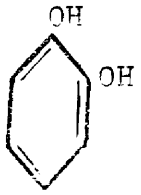
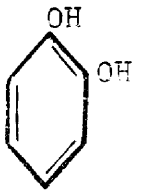
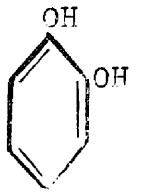
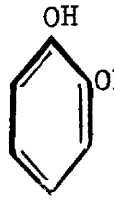
Amine	Rabbits intraven. M.L.D. mg./Kg.	Rats Subcutan. M.L.D.-50 mg./Kg.	Guinea Pigs subcutan. M.L.D. mg./Kg.	Times weaker than Epinephrine	Remarks
1. $C_6H_5CH_2.CH_2NH_2$	60 (21) 40-50 (32)			160 (53) 133 (15)	No tachyphylaxis (24) Not active orally (32)
2. $C_6H_5CH_2.CHNH_2.CH_3$	25 (21)			425 (15)	Tachyphylaxis (15) Active orally, pressor rise lasts longer than compound 1 (15)
3. $C_6H_5CHOH.CH_2NH_2$	80 (32) 90 (33)		1000 (24)	250 (24)	No tachyphylaxis (24) Not active orally (32)
4. $C_6H_5CHOH.CHNH_2CH_3$	75 (33)		800 (33)	60 (15)	Tachyphylaxis (32,21) Active orally (32)
5. 	0.1 (30)			1	No tachyphylaxis Not active orally
6. 	1 (26)			41 (15) 40 (54)	No tachyphylaxis (15) Pressor response not distinguished from compound 5 in equiv. doses (26)
7. 		0.5 (12)		1.2 (12)	No tachyphylaxis (12, 54)
8, 		8 (12)		14.9 (25) 12 (12)	No tachyphylaxis (12,54) Active orally (30)

Table 4

Effect of increasing carbon chain beyond three carbons

Amine	Toxicity-HCl salt(33)		Activity
	Guinea pigs subcutan. M.L.D. mg./Kg.	Rabbits intraven. M.L.D. mg./Kg.	
1. $C_6H_5CHOH.CHNH_2.CH_3$	600	75	Good pressor, 1/60 as active as l-epinephrine (15)
2. $C_6H_5CHOH.CHNH_2.C_2H_5$	250	60	Low activity in dogs (33) and pithed cats (32). 1/2262 activity of l-epinephrine in cats (15)
3. $C_6H_5CHOH.CHNH_2.C_3H_7$	300	40	Depressor in cats (15)
4. $C_6H_5CHOH.CHNHCH_3C_3H_7$		35(32)	Depressor in cats (15)
5. $C_6H_5CHOH.CHNH_2.C_4H_9$	250	20	Depressor in cats (15). 10mg./Kg.in dog caused fall in b. pressure, followed by a grad. rise to a new level as much above as the fall was below normal (33)
6. $C_6H_5CHOH.CHNH_2.C_6H_{11}$	450	10	Depressor in cats, 10 mg. killed cat (15) No pressor activity (33)
7.  $CHOH.CHNH_2.CH_3$	175	33	3/5th as active as compound 1 (33)
8.  $CHOH.CHNH_2.C_2H_5$	150	25	No pressor effect (33)
9.  $CHOH.CHNH_2.C_2H_5$			All doses tried (0.05-0.5 mg./Kg.) produced only a fall in blood pressure in cats (15)
10.  $CHOH.CHNHCH_3.C_2H_5$			Depressor (31)

are inactive orally in man.

Piness, Miller and Alles (36) were desirous of determining what phenylethanolamine (XIII) lacked structurally to make it orally active. Since it differed from ephedrine (V) by a methyl group in the side chain and on the amino group, they investigated phenylethylamine (XIV) and two of its methyl substituted derivatives (XV) and (XVI).

$CH_2 \cdot CH_2NH_2$

(XIV)

$CH_2 \cdot CH_2NHCH_3$

(XV)

$CH_2 \cdot CHNH_2 \cdot CH_3$

(XVI)

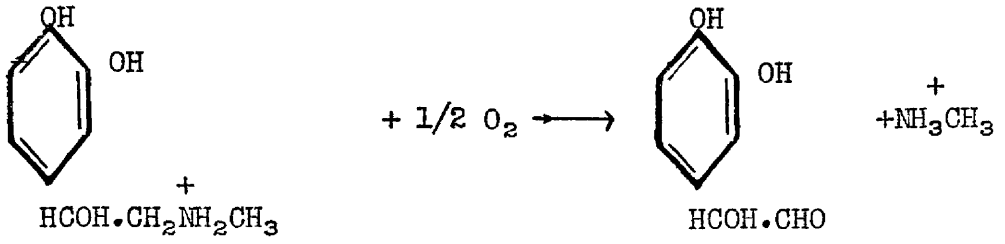
They found (XIV) and (XV) to be inactive orally, while (XVI) possessed oral activity and its action was of greater duration than that of the other two. From this they also concluded that it is the methyl group on the side chain which is responsible for oral activity.

Hartung et al (21) further substantiated these findings by showing that the extension of the side chain of β-phenylethylamine conferred oral activity whether the methyl group is substituted on the α or β carbon.

Several groups of investigators have studied the enzymatic inactivation and the fate in the body of a number of pressor amines. Their results have further contributed possible explanations of the effect of structure on the oral activity, relative toxicity, duration of action, etc. of these compounds.

Blaschko (37) showed that there is present in extracts of liver, intestine and other tissues of mammals an enzyme which catalyzes the oxidation of epinephrine. This enzymatic oxidation in the presence of cyanide (which prevents autoxidation and secondary reactions) involves the uptake of one

atom of oxygen per molecule of epinephrine. Richter (38) then found that in this oxidation of epinephrine, as well as in that of other related primary, secondary and tertiary pressor amines containing the amino group on the end of a two carbon atom side chain, an aldehyde and ammonia or a lower amine is produced in each case. He therefore explains the oxidative deamination of epinephrine by the equation,



and that of the other amines studied by analogous reactions. This reaction is chemically similar to the oxidative deamination of tyramine which Hare (39) studied and which he found to be catalyzed by an enzyme present in liver. The results of Weinstein and Manning (41) substantiate this type of epinephrine oxidation. They found that when epinephrine is injected into rabbits, an acid with properties similar to protocatechuic acid is excreted in the urine. Thus under these conditions, the epinephrine also appears to be inactivated by oxidation in the side chain, possibly by Blaschko's amine oxidase.

On the other hand Richter (68) found that epinephrine, as well as corbasil ($3,4\text{-}(OH)_2C_6H_3CHOH.CH_2NH_2.CH_3$) and epinine ($3,4\text{-}(OH)_2C_6H_3CH_2.CH_2NHCH_3$) are eliminated after oral administration to men chiefly by conjugation (phenolic ester) instead of by oxidation by amine oxidase. From this he inferred that conjugation is more rapid than oxidation by amine oxidase and probably is the main physiological method by which these compounds are inactivated in the body. He explains the excretion of catechuic acid

observed by Weinstein and Manning as due to their heating the rabbit's urine with alkali. Since protocatechuic acid may be formed from epinephrine by heating with alkali, this acid may have been produced from epinephrine in the urine.

Blaschko, Richter and Schlossmann (43) studied the relationship of structure to inactivation by amine oxidase in vitro in a series of sympathomimetic amines. They were able to show that, (a) certain groups which are present in the epinephrine molecule, namely, the hydroxyl in the side chain, the phenolic hydroxyls and the N-methyl group are not essential for the enzymatic oxidation; (b) only those amines which like epinephrine contain the amino group on the terminal carbon of a two membered side chain are oxidized; and (c) those amines which differ from epinephrine only in the presence of an additional CH_3 group in the side chain are not oxidized. They therefore concluded that the $\equiv C-CH_2-N=$ is essential for the oxidation. Further studies by this group of workers (40) on a more extensive series of sixty-six amines confirmed their previous observation that only compounds containing the amino group at the end of the hydrocarbon chain are oxidized. In the case of ephedrine and other isopropylamine derivatives, their resistance to the action of the enzyme is not due to their lack of affinity for the enzyme, since they inhibit the oxidation of other amines by competing for the enzyme (competative inhibitors).

In addition to amine oxidase Beyer (44) also studied a second enzyme, phenol oxidase. This enzyme was found to catalyze, in vitro, the oxidation of compounds containing an isopropylamine side chain when these compounds also contain a para phenolic hydroxyl, but not when this group is lacking. Thus compounds like ephedrine, propadrine and benzedrine which are active orally and which contain an isopropylamine side chain, but no phenolic hydroxyl, are not inactivated by either amine oxidase or phenol oxidase

in vitro.

Supplementing these observations are a number of studies conducted in vivo. Richter (56) observed the excretion of ephedrine following its administration. Beyer and Skinner (55) found that about half a given dose of benzedrine is excreted as such by the dog's kidneys over a period of forty-eight hours; but if kidney function is impaired by CCl_4, the excretion of the drug becomes as much as 100% of the given dose. Ascorbic acid also plays a part in the destruction of benzedrine since its feeding to dogs reduces the excretion of this amine to about 35% of the controls, depending on the vitamin C content of the animals (79). Beyer and Lee (80) investigated a number of non-phenolic compounds related to benzedrine in order to determine whether they are excreted in the urine or totally inactivated in the body. They found that the compounds in which the amino group is not on the terminal carbon atom of the side chain are excreted in the urine after oral administration to men. These compounds are also not deaminated by amine oxidase in vitro. β-phenyl-n-propylamine and γ-phenyl-n-propylamine, having the amino group on the terminal carbon, were not excreted in more than occasional traces by either humans (orally), or by dogs injected subcutaneously in order to rule out the destruction of these amines before their absorption into the body. However, the impairment of liver function by CCl_4 or hydrazine caused these two amines to be excreted to some extent, thereby indicating that the liver is a principle site of inactivation of these amines whether or not it be entirely by amine oxidase.

From their results together with what has been found to be true for other similar sympathomimetic amines, Beyer and Lee (80) offer the following explanation of oral activity and fate in the body of these agents.

> "In this particular group of amines the position of the amino group on the side chain determines whether the compound shall be

> active orally and excreted by the kidneys, or inactive orally and totally inactivated in the body enzymically or otherwise. The compounds that do not have the amino group on the terminal carbon atom are active orally, not because they are not broken down by the digestive juices, but because on being taken into the body they are not deaminated at once when brought by the portal system to the liver. This being the case they are then carried to all parts of the body. Since they remain in the blood stream, at least to some extent, for a long period of time they are cleared from the blood by the kidneys and appear in the urine. Part of the drug remaining in the tissues is inactivated by some system as the ascorbic-dehydroascorbic acid system.
>
> "Confirming this interpretation, these compounds having an amino group on the terminal carbon atom have no physiological effect when taken orally. Also they do not appear in the urine as such even when injected subcutaneously. It seems likely then that, administered orally, instead of being broken down in the digestive tract the compound is absorbed, deaminated to some extent in the intestinal wall, where amine oxidase has been shown to be present, and the rest brought to the liver where the enzymatic oxidation is complete."

Enzymic activity has also figured in several other theories concerning sympathomimetic activity. Gaddum and Kiviatkowski (66) proposed the theory that ephedrine potentiates the action of epinephrine by inhibiting amine oxidase and thus preventing the destruction of the epinephrine. This is similar to the view that eserine potentiates acetylcholine action by inhibiting choline esterase. Likewise the tachyphylaxis of ephedrine may be due to the blockage of the motor receptors by ephedrine which thus excludes the chemical transmitter through whose preservation from the enzyme the earlier doses of ephedrine produce their effect.

Tainter and Morton (67) found that amines containing no catechol nucleus, nor a meta phenolic hydroxyl group, show vasoconstriction when perfused through the hind legs of cats only if epinephrine is added to the perfusion fluid. They therefore proposed the hypothesis that these compounds (such as ephedrine and tyramine) produce at least part of their action by blocking the enzymes, or other local tissue mechanisms, which inactivate epinephrine. They thereby permit increased local concentrations of this hormone liberated from the sympathetic endings or derived from the blood stream, which causes stimulation.

V. Effect of the Alcoholic Hydroxyl in the Side Chain

A comparison of similar compounds differing only by a hydroxyl group in the side chain indicates that the presence of the alcoholic hydroxyl group on the carbon atom bearing the aromatic group generally increasses pressor potency and decreases toxicity (table 5).

In addition Chen, Wu and Henriksen (32) claim that this group is essential for mydriatic action. Thus β-phenylethylamine which is devoid of this group has no mydriatic action on the rabbit pupil, while phenylethanolamine shows mydriatic action.

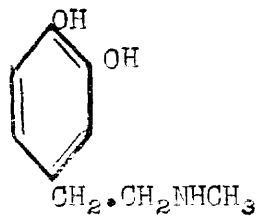
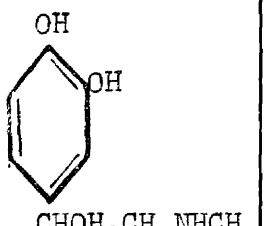
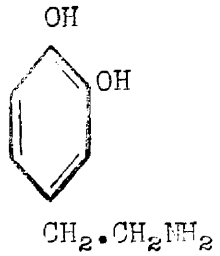
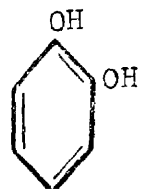
VI. Modification of the Primary Amino Group

Among the natural products belonging to the sympathomimetic group can be found primary, secondary and tertiary bases. The physiological difference between these respective types has also been investigated.

Barger and Dale (4) were among the first to study this phase of pressor activity. They reported that when β-phenylethylamine (VI), tyramine (IV), and phenylethanolamine (XIII) are converted into their corresponding secondary methylated bases there is no appreciable change in pressor potency. However in the case of 3,4-dihydroxyphenylethylamine, they found that methylation to the secondary amine increases the activity fivefold. Other workers have reported that methylation does affect pressor activity. Chen, Wu and Henriksen (32) showed that conversion of phenylethanolamine and phenylbutanolamine into their corresponding methylated secondary amines decreased pressor action. They stated that except in the case of phenylethanolamine, the other primary amines which they studied are less toxic than the corresponding secondary amines. Tainter (15) found that $C_6H_5 \cdot CH_2 \cdot CH_2NH_2$ is 1/83

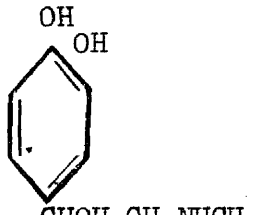
Table 5

Effect of the alcoholic hydroxyl group

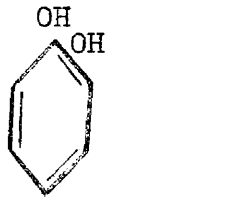
Amine	Toxicity-rabbits intraven. M.L.D. mg./Kg.	Times weaker than epinephrine	Remarks
1. $C_6H_5CH_2 \cdot CH_2NH_2$	40-50 (32) 60 (21)		2 mg./Kg. intraven. in rabbits produced a fall followed by a slight rise (24)
2. $C_6H_5CHOH \cdot CH_2NH_2$	80 (32)	250 (24)	1-4 mg. produced a sharp rise. Max. rise greater than compound 1 (24)
3. $C_6H_5CH_2CHNH_2 \cdot CH_3$	25 (21)	425 (15)	
4. $C_6H_5CHOHCHNH_2CH_3$	75 (33)	60 (15)	
5. 		12 (11) 10 (58)	Duration of action twice that of compound 6 (11)
6. 		1	
7. 		65 (7)	
8. 		1.2 (12)	

as active as epinephrine while $C_6H_5 \cdot CH_2 \cdot CH_2NHCH_3$ acts irregularly in cats, producing only depression in two out of five cats.

Tainter (12) has studied the effect of converting epinephrine into the corresponding primary amine (arterenol). He states that l-epinephrine is 1.2 times as active as dl-arterenol on blood pressure in urethanized cats. However since dl-epinephrine is only 1/2 as active as l-epinephrine, dl-epinephrine is only 2/3 as active as dl-arterenol. Since l-epinephrine is 3.3 times as toxic as dl-arterenol and is only 1.2 times as active, arterenol has almost 3 times the therapeutic index of l-epinephrine. Moreover, the duration of action of arterenol is greater than that of an equivalent dose of l-epinephrine. The removal of the methyl group of epinephrine also influences its mechanism of action. Thus though



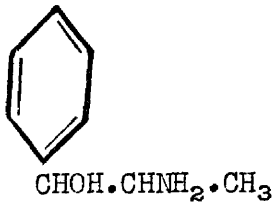
epinephrine



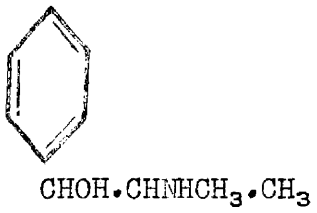
arterenol

ergotamine (12) and yohimbine (59) reverse the pressor action of epinephrine, they do not reverse that of arterenol.

According to Chen, Wu, and Henriksen (32), the methylation of dl-propadrine to produce dl-ephedrine decreases the activity and increases the toxicity by about 20%.



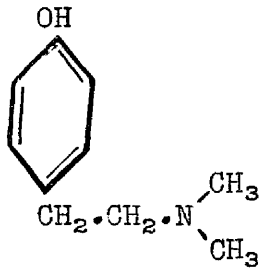
propadrine



ephedrine

Tainter (15) on comparing 3,4-dihydroxypropadrine and 3,4-dihydroxy-ephedrine found that the former is more than three times as active as the latter, while Chen and Chen (54) found the activity of the former to be ten times as active.

The introduction of a second methyl group to produce a tertiary amine works to further disadvantage. Thus hordenine shows a mixed action consisting of a nicotine-like effect on ganglia and sympathetic stimulation. It customarily gives a rise of pressure which is poorly sustained and which produces an irregular form of curve (10).



hordenine

methylephedrine

Methylephedrine has been found to be less active, and more toxic than ephedrine, and no longer has a mydriatic action (32). Curtis (61) states that methyl-ephedrine is far less active in pithed cats than ephedrine although it still dilates the cat bronchi with the same efficiency. Pak and Read (62) found that in cats the pressor action of methylephedrine is approximately 1/10 that of ephedrine but accelerates the heart less; while in moderate doses it does not, like ephedrine, stimulate the central nervous system, is less toxic in rabbits and dogs, and is still effective by oral administration.

The use of higher alkyl groups in place of methyl is again a step in the wrong direction. In the phenylpropanolamine series $C_6H_5CHOH\text{-}CHNHR.CH_3$, when $R=C_3H_7, C_4H_9$ or C_5H_{11} the resultant compound has a depressor effect in pithed cats, and an increase in toxicity results as R increases from CH_3 to C_5H_{11} (intraven. in rabbits) (32). Thus when the number of carbon atoms in

the alkyl group attached to the nitrogen increases beyond two, a depressor action becomes the predominate feature and the toxicity in rabbits and the depressant action on the frog heart increases.

Barger and Dale (14) observed that the conversion of the amino group to a quarternary ammonium salt produces compounds with nicotine-like actions.

Kanao (63) found that if the alkyl group on the nitrogen is sufficiently large, the compound assumes anesthetic properties. Thus $C_6H_5CHOH.CH_2NHR$ is anesthetic when R equals isobutyl or phenyl. $C_6H_5.CHOH.CHNHR.CH_3$ is non-anesthetic when R equals ethyl or propyl, but is anesthetic when R equals allyl, isobutyl, isoamyl, benzyl, p-aminobenzyl, furfuryl or citral.

Chen, Wu and Henriksen (32) have considered alkyl substituents on the amino group as a factor in producing mydriasis in the rabbit pupil. They observed that if the alkyl groups on the alpha carbon and on the amino group is methyl or ethyl, mydriatic action remains. Further lengthening of either of these substituents makes this specific action disappear. Both primary and secondary amines may dilate the pupil, but the formation of a tertiary amine abolishes this property.

PROPADRINE SERIES

I. Review of Propadrine

Phenylpropanolamine (XVII) is also known as norephedrine in the

$HCOH.CHNH_2.CH_3$

(XVII)

French literature, as propadrine in America, and as mydriatin, the latter being the name under which it was patented by Nagai (72).

It was first isolated from a natural source in 1928 by Smith (73) who obtained the d-pseudo isomer from the Ephedra species. In 1930 the l-isomer was obtained by Seizo and Kanao (74) from Ma Huang, and by Wolfes(75) from the European Ephedras.

Hirose (76) first observed its pressor effects in animals, and found that as a pressor drug it was weaker than dihydroxyphenylethanolamine. He also observed that the racemic mixture dilated the human and frog pupil. Amatsu and Kabota (77) from their work concluded that its action is quantitatively the same as that of ephedrine. This was later confirmed by Hartung and Munch (21) who found that it is as active as l-ephedrine, produces in substantially every respect the characteristic responses of ephedrine, is active orally, and when given intravenously to dogs produces a prolonged rise in blood pressure.

1. Classification of action. Tainter (15) observed that in cocainized cats, the pressor effects of propadrine are almost completely abolished,

while those of epinephrine are definitely sensitized. Ergotamine reverses the pressor action of epinephrine but completely abolishes that of propadrine without reversing it. From this it follows that propadrine is not sympathicotropic since it does not act like epinephrine. Neither is it a pure musculotropic stimulant since cocaine and ergotamine do not decrease the reactivity of drugs acting purely on muscle. For these reasons propadrine must be classed as a pseudosympathicotropic drug. The abolition of its pressor action by ergotamine should not be interpreted as evidence that propadrine stimulates the sympathetic vasoconstrictors, but has no action on vasodilators since it can be readily seen that this interpretation would be inconsistent with the results after cocainization where the vasoconstrictors are hypersensitive and where the drug is inactive.

This pseudosympathicotropic nature of propadrine was substantiated by Levy (78) who worked with cocainized animals and with dogs whose vasoconstrictor endings were paralyzed by yohimbine. In both instances the pressor action of propadrine was only diminished. From these results he also concluded that propadrine was not a pure sympathicotropic drug. He also concluded that while propadrine could be considered as having both sympathicotropic and musculotropic properties, at least as to its point of vasomotor site, it is probably more sympathicotropic as shown by the diminution of its pressor action and complete abolition of renal vasoconstrictor action after yohimbine, as well as the persistence of pressor effect, though diminished, in the cocainized animal.

2. Pressor effects. Various authors agree that propadrine is as active as ephedrine on the blood pressure (23,78,81,30) when injected intravenously, and Hartung (21) reports it to be active orally when given in adequate dosage. Intravenously in dogs, its pressor ratio to epinephrine has been stated to be about 390 (69) and 250 (78). In urethanized cats, Tainter (15) found that 1 mg./Kg. of racemic propadrine caused a median rise

of 20% which lasted 10 minutes, and produced no consistent change in pulse rate which he considered suggestive evidence against a sympathicotropic action. Its pressor ratio to epinephrine had a median value of 60 indicating it to be more active in cats than that indicated for dogs in the above studies. Since in his work an adequate number of animals was used, with good agreements between them, he feels that the ratio of 60 correctly indicates its degree of activity. Though subcutanously or intramuscularly 10 mg. produced a moderate prolonged rise of blood pressure, 20 mg. injected into a loop of intestine in situ, produced no rise. It is said to exhibit, like ephedrine, tachyphylaxis, i.e., each successive dose produces a smaller rise in pressure than previous doses (32,78,21,69) though Tainter (15) in his experiments on cats observed that two injections of 1 mg. spaced one hour apart gave reproducible results.

3. Optical isomers. The six optical isomers of propadrine were separated by Kanao (82) in 1928. According to Hirose (cited by Chen and Schmidt - 83) the order of activity of these isomers is as follows:

d-pseudo > dl=l, d < l, d-pseudo > l-pseudo < l.

Chen, Wu, and Henriksen (32) point out that the dl-isomer is a stronger pressor than dl-ephedrine and attributes it to the absence of the methyl group on the amino nitrogen. The d-pseudo isomer is weaker than the l or dl-ephedrine, but stronger than the d-pseudo ephedrine. Launoy and Nicolle (84) state that racemic propadrine is more active than racemic ephedrine, and that the l- form is three times as active as l-ephedrine.

4. Cardiac action. Levy (78) reported that in situ, weak doses of racemic propadrine slowed the heart due to stimulation of the vagus center. In the atropinized animal, cardiac stimulation with an increase in the amplitude of auricular and ventricular contractions was observed. With

larger doses or repeated small doses, cardiac depression with a diminution of amplitude was the result; the diminution being transient if the dose is small enough, but prolonged and accentuated with stronger doses, giving place at times to auricular ventricular fibrillation. 5 cg. injected into the lymph sac of frogs stopped the heart in diastole after two hours, while a 1% solution applied locally slowed the frequency and diminished the amplitude. Chen, Wu, and Henricksen (32) found that perfusion of frogs hearts produced no increase of heart rate, and 1:1,000,000 was the minimal concentration causing depression. 2 to 5 mg. increased the amplitude of the beat of isolated rabbits' auricles (69) though epinephrine produced a bigger effect in doses over 1,000 times as small.

In general it may be stated that its cardiac action is stimulating in small doses but depressing in larger doses. Its action on the heart vessels, as well as on the bronchi and intestine indicate a close relationship to ephedrine.

5. Mydriatic action. Miura (85) claimed it to have a strong mydriatic action in men. The pupil begins to dilate in 20 to 30 minutes and mydriasis lasts twenty-four to thirty-six hours with the accomodation unimpaired. A local application of a M/20 solution of the d-pseudo isomer dilates the pupil of albino rabbits' eyes (32) with preservation of the light reflex.

6. Action on smooth muscle. Hasama (23) reported that in large doses propadrine can dilate the intact, but constricts perfused bronchi. Levy (78) stated that perfusion into the bronchi of doses of 0.5 to 0.1 mg. produced vasoconstriction, and did not modify the vasodilatation produced by epinephrine. Alles and Prinzmetal (86) observed a slight bronchodilation in dogs and cats. Tainter et al (87,25) found only a bronchoconstrictor response in perfused guinea pig lungs and practically no dilator action on

bronchial spasms produced by histamine in dogs. He therefore regarded it as giving negative bronchial effects.

In 1:75,000 concentrations it produces a lessening of the tonus and a diminution in amplitude and frequency of peristalsis of the isolated rabbit intestine (78). The pregnant cat uterus in situ is contracted while the non-pregnant uterus is slightly relaxed (69). It generally augments isolated rabbit and guinea pig uteri (32,88).

7. Toxicity. Its toxicity has been determined under various conditions. Chen, Wu, and Henricksen (32) state that propadrine has an M.L.D. of 75 mg./Kg. for rabbits (intraven.) and is thus less toxic than ephedrine which has an M.L.D. of 60 mg./Kg. Other toxicity reports are summarized in the following table:

TABLE 6

Toxicity of propadrine

Animal	Fatal dose-mg./Kg.		
	Subcutan.	Intraven.	Intraperiton.
Rat	700 (23)	85	175 (4)
Guinea pig	350,(20) 600 (4)		
Rabbit		75-90	
Dog			over 500 (4)

8. Effect on the blood sugar of rabbits. This study was carried out by Krantz and Hartung (89) on rabbits which had been starved twenty-four hours before administration of the drug. A maximum rise or fall of blood sugar occurred 30 to 70 minutes after intravenous injection. It was found

that 20 to 30 mg./Kg. influenced the blood sugar. However the results were variable and the influence was not marked, being either hypo or hyperglycemic. Nevertheless the following trends were noticed.

a. Thirty minutes after injection the tendency of activity was toward a mild hyperglycemia in most cases, approximately 60% resulting in a rise of about 10 mg./100 cc. of blood.

b. Seventy minutes after injection the tendency of the blood sugar level was to fall below the fasting level, most of the determinations indicating a fall of about 18 mg.

When administered subcutaneously, a dose of 100 mg./Kg. was without appreciable effect on the blood sugar level, as was an oral dose of 200 mg./Kg.

9. Potentiation of the pressor effect of epinephrine. Munch and Hartung (29) conducted experiments on dogs anesthetized with morphine and chloretone in order to determine the effect of a single dose of propadrine and related compounds upon the subsequent pressor effect of epinephrine. It was found that propadrine and ephedrine in doses of 1 mg./Kg. intravenously potentiated or increased the subsequent epinephrine rise 2.75 times. An increase in dosage of these drugs increased this potentiation effect. Phenylethanolamine and phenylbutanolamine produced no similar effect in the same dosage, and from this these investigators concluded that the ability to potentiate the pressor responses of epinephrine was characteristic of the phenylpropanolamine compounds.

The results of oral administration were more variable than those obtained with intravenous injections. It appeared that potentiation was not produced by the doses employed (up to 75 mg.). Those doses failing to show such an effect also failed to show any definite evidence of an increase in blood pressure. However, 100 mg./Kg. orally produced a definite increase in the blood pressure of dogs and the results suggested the

possibility of potentiation. They concluded that the oral administration in the doses employed did not definitely produce potentiation. Ephedrine produced similar results on oral administration. A clinical report by Csepar and Doleschall (90) reported that the administration of ephedrine caused a subsequent injection of epinephrine to produce a greatly potentiated increase in blood pressure.

This potentiation effect was also observed by Tainter (15) who observed in addition that arterenol was similarly sensitized by propadrine. Hence this alteration in functional response is not peculiar to epinephrine alone, but presumably involves the sympathetic receptors.

10. Bio-assay of propadrine. Githens (81) attempted to find a suitable method of assaying propadrine and ephedrine. Although their qualitative actions have been elucidated fairly well, none of these actions lend themselves to accurate quantitative analysis. Their actions differ so widely, quantitatively at least, from one animal to another, and all are so markedly influenced by slight experimental differences which are not readily analyzed, that it is difficult to obtain quantitative determinations by comparing the action on one animal directly with that on another. Most biologically assayed drugs acting on the autonomic system, such as epinephrine, are assayed by comparing the results obtained on a particular animal or tissue with those obtained on the same animal or tissue with a standard solution of the drug being tested. In the case of propadrine and ephedrine however, this method is impractical since their effects are altered or reduced by previous administrations (tachyphylaxis), so that whichever sample is first employed will appear to be the stronger. This reduced effect on repeated administrations is true not only of their pressor actions but also of their effects on isolated tissues. Moreover, there is no fixed relation between the rise caused by the first and

by subsequent doses. This fact makes it impossible to standardize the test animal by giving a definite dose of a standard preparation and to base the assay on the relation between the rise caused by this and the rise following the administration of a solution of unknown strength. If the doses are much smaller than that giving a maximum response, this tachyplaxis tends to become less with repetition of the dose, and eventually subsequent doses may give substantially identical effects, although the response is never as regular as it is with repeated injections of the same dose of epinephrine.

In the attempt to develop a method of biological assay which would give quantitative results within 10 to 20%, Githens investigated four methods.

a. The mydriatic action on the isolated frog's eye. Although mydriasis was caused by all dilutions of propadrine down to 1:8,000 there was no relation between the strength of the solution and the degree of mydriasis. In some cases a weaker solution caused more dilatation than a stronger solution even when the comparison was made between the two eyes of the same frog.

b. Action on the isolated uterus of the guinea pig. There was a lessened response with repeated doses, the reduction being at the same time irregular. This method did not seem promising for quantitative studies.

c. Pressor relation to epinephrine. Dogs anesthetized with chloretone were used. Each dog was standardized by determining its sensitivity to epinephrine, and the pressor effect of a single dose of the drug was compared to the pressor effects of graded doses of the epinephrine given previously. The strength of the drug could thus be expressed in terms of its relation to epinephrine. It was found that

different dogs vary markedly in their response to propadrine and ephedrine. In a series of forty dogs no quantitative relationship was found between the dose and the effect. For example, the 1600 mg. dose caused a rise of only 30 mm. of mercury while another dog given only 390 mg./Kg. showed a rise of 110 mm. The relation was no more exact when the rise was calculated in terms of per cent of the original blood pressure. This variation of responsiveness in individual animals was noted by other workers both with epinephrine and ephedrine. Using forty-two dogs in the test with propadrine the relation varied from 1:125 to 1:1000, the average being 1:495. Moreover, the variation of the animals to epinephrine did not parallel that to propadrine.

d. Effect of repeated doses on the blood pressure. With this method originally devised by Feng and Read (94), it was possible to obtain results within 20 or even 10% with only one or two dogs in each test. Anesthetized dogs were given repeated doses of ephedrine or propadrine intravenously at intervals of an hour. Each dose contained 1 mg. of a standard solution or an approximately equal amount of solution in each test. The dose was not adjusted to the weight of the dog as no relationship between this and the response to a fixed dose was found. The dog was given first 1 mg. of the standard and the rise measured. At the end of an hour, it was given the solution under test, and at the end of another hour, the standard was given once more in the same dose. This was continued at hourly intervals, preferably four doses of each being given. The averages of all the doses of each sample were then taken. If there was a discrepancy of more than 20% between them, it was fairly safely concluded that this represented a real difference in the potency of the solution. This method takes advantage of the same amount of tachyphylaxis induced by small doses

of the drug given at long intervals. The following is an illustrative example in which two 1% solutions (A and B) of the same lot of propadrine were assayed according to this method. In some cases the rise from the first injection was unduly large, and in such cases this rise was excluded in the calculation. The injections were made on the same animal.

Time	Sample	Dose-mg.	Rise-mm.
10:55	A	1	22
11:55	B	1	12
13:00	B	1	12
14:00	A	1	10
15:00	A	2	14
16:00	B	2	14

Average rise of injections of A — 13 mm.

Average rise of injections of B — 12 mm.

Since the result is within 10% the solutions are approximately of the same activity.

11. Clinical studies. Several references to the clinical use of propadrine appear in the literature. Chen, Wu, and Henricksen (32) administered it orally in 50 mg. doses to two individuals and found that it produced a maximum rise of 16 mm. and 30 mm. of mercury in the systolic blood pressure. Stockton, Pace, and Tainter (91) observed that topical application of a 3% solution to the nasal mucosa of patients with acute or or chronic sinusitis produced constrictor effects equal to that of ephedrine and synephrine, and showed no evidence of local irritation, whereas ephedrine produced burning and irritation in 25% of the cases. Black (92)

reported its use in the symptomatic control of hay fever and in asthma in a series of one hundred and thirty-one patients. He found that though it is only equally as effective as ephedrine it is relatively free from the side effects such as insomnia, nervousness, motor restlessness, and nausea commonly experienced following the administration of ephedrine. This obviates the necessity of combining with it a sedative and makes it possible to use it at frequent regular intervals. Its use every three or four hours gave more relief to the patient suffering with urticaria and neurotic edema (angio) than any other medication that he has found. Boyer (93) administered as much as 3/4 gr. of the hydrochloride every two hours for five days or more to a series of forty-four patients suffering from asthma, without any toxic manifestations. 19% of the patients reported it to be inferior to other forms of medication, 11% claimed it to be equally efficacious to previous medication, and 8% reported it to give the greatest symptomatic improvement. Clinically, bronchial spasm, rhinitis, and sneezing were relieved but in Boyer's experience, its outstanding value is the absence of side reactions encountered with the use of ephedrine. It may be safely used in cases of hypertrophy of the prostate gland where retention of the urine is produced by ephedrine. In children it does not produce restlessness, or walking or talking in their sleep. Tachycardia and palpitation were not observed as in the case with ephedrine. He therefore concludes that propadrine is a satisfactory and valuable therapeutic agent in the treatment of allergic manifestations.

II. Ring Substituted Propadrines

A number of ring substituted propadrines have been prepared and their physiological properties studied. The effect of introducing various

substituents into the phenyl group of propadrine is summarized in table 7.

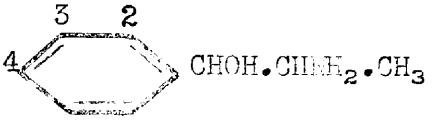
p-Hydroxypropadrine is superior to the unsubstituted compound since it is more active and less toxic, while the m-hydroxy compound is still more active though also more toxic. The increase in pressor activity produced by a meta hydroxyl substituent is also demonstrated in the case of 3-hydroxy-4-methylpropadrine which is more active than 4-methylpropadrine. 3,4-Dihydroxypropadrine, containing the two phenolic hydroxyls in the same positions in which they occur in epinephrine, is the most active member of this series (5 to 12 times as active as propadrine) and the most toxic (about 7 times as toxic as propadrine in rabbits). In anesthetized dogs it produces blood pressure tracings indistinguishable from that of epinephrine except as to dosage. Tainter (12) states that the major part of its circulatory action is of a true sympathicotropic nature. The introduction of an ortho hydroxyl decreases activity and increases toxicity. Thus o-hydroxypropadrine is less active than propadrine while 2,4-dihydroxypropadrine is inactive in small doses and depressor in large doses (8 mg.) With none of the active phenolic compounds was tachyphylaxis observed by Hartung and co-workers (30).

The introduction of a methyl group into the meta position of both propadrine and p-hydroxypropadrine makes the new compound decidedly more toxic and less active. A para methyl group exerts a similar effect.

As indicated in table 7, the other substitutions into the aromatic nucleus of the propadrine molecule, which have been investigated, produce no decided improvements of the physiological properties of the unsubstituted compound.

TABLE 7

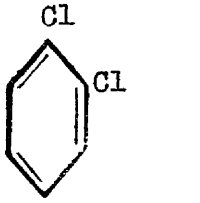
Ring substituted propadrines



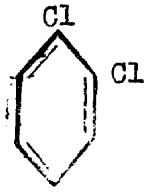
Substituents			Toxicity rabbits intraven. M.L.D. mg./Kg.	Times weaker than epinephrine	Pressor Ratio to propadrine (30)	Duration of Pressor rise cats min.(15)
2	3	4				
H	H	H	75 (32) 75 (33)	60 (15)	1	10
H	H	OH	130 (32) 100-125 (30)	67 (15)	1.5	11
H	OH	H	16 (30)	11.5 (15)	3	8
OH	H	H	40 (30)	200 (15)	Less than 1	7
H	OH	OH	11 (30)	4 (54) 12 (12)	12 or more	4 (12)
OH	H	OH	12 (30)	inactive (30) 8 mg.-depressor (12)		
H	H	CH_3	33 (33)	5 mg. gave only 18% rise, larger doses-fall followed by use (15)	0.6	11
H	CH_3	H	30-35 (20)	168 (15)	0.20 (20)	22
H	H	OMe	35 (30)	Fall of blood pressure (15)	0.5	17
OMe	H	H	25 (30)	226 (15)	1	9
OMe	H	OMe	21 (30)	greatest use 11% dose greater than 10 mg.-depressor(15)	1	12
H	CH_3	OH	20 (30)	288 (15)	2	11
H	OH	CH_3	90 (30)	151 (15)	2	12
H	H	C_6H_5	17.5 (30)		trace of activity (20)	
H	H	Cl	25 (10)	248 (15)	0.04 (20)	6

REVIEW OF THE HALOGEN RING SUBSTITUTED PRESSOR AMINES

3,4-Dichloro-ω-aminoacetophenone hydrochloride (XVIII) and its corresponding alcohol (XIX) were found by Glynn and Linnell (64) to possess pressor action, though much less than that of epinephrine. Compound (XVIII) is



(XVIII)



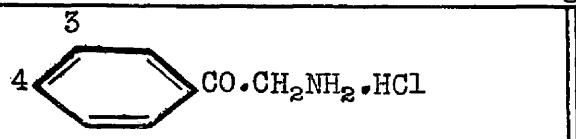
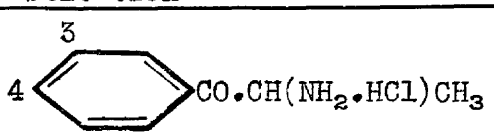
(XIX)

about 1/500th and (XIX) 1/200th to 1/250th as active as epinephrine in spinal cats. They state that: "the toxicity of α-3,4-dichlorphenyl-β-aminoethanol hydrochloride by intravenous injection into mice is about 1/240th that of l-epinephrine. Doses given orally (by stomach tube) indicated that the compound is active when administered in this way, and it must be emphasized that the side chain does not contain a third carbon atom to which oral activity has been attributed." The pressor activity of this compound was abolished by a previous injection of cocaine.

Edkins and Linnell (65) studied the effect on physiological properties of halogen substitution in ω-aminoacetophenone and α-aminopropiophenone. Their results are summarized in table 8. Compared with the unsubstituted compounds, both of the 3-Cl,4-OH compounds are considerably weaker. The position of the halogen in the phenyl nucleus seems to be an important factor. Thus the introduction of chlorine or bromine into the meta-position almost doubles pressor activity, while no difference is

TABLE 8

Effect of Halogen Substitution

							
Substituents		Relative Pressor Activity Cats	Toxicity-Mice intraven. mg./gm.	Substituents		Relative Pressor Activity Cats	Toxicity-Mice intraven. mg./gm.
4	3			4	3		
H	H	10	.350	H	H	19	.200
Cl	Cl	9		OH	Cl	3	.700
OH	Cl	3	.500	Br	H	6	.150
Cl	H	8	.300	Cl	H	7	.175
Br	H	5	.175				
H	Cl	17	.200				
H	Br	18	.200				

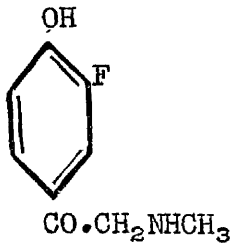
observed between the effects of chlorine and bromine. On the other hand, when the halogen occupies the para position, a decrease of activity, especially marked in the α-aminopropiophenone series, is produced. The 3,4-dichloro compound has a similar activity to the unsubstituted amino ketone and hence the presence of the para halogen has counterbalanced the increase in activity due to the presence of the meta-substituent. Similarly the para-hydroxyl more than negativates the increase of activity produced by a meta halogen. Contrary to other series previously discussed, both α-aminopropiophenone hydrochloride and the alcohol derived from it were found to be more active than ω-aminoacetophenone hydrochloride and its reduction product. This is an example of compounds with a 3 carbon side chain being more active than those with only 2 carbons in the side chain.

A consideration of the toxicities of these compounds reveals little correlation between toxicity and constitution. Both 3-Cl,4-OH-derivatives are the least toxic of the substances considered. The 4-Br-derivative is more, and the 4-Cl-derivative is less toxic than the 3-Cl-ω-aminoacetophenone hydrochloride. 4-Br-α-aminopropiophenone hydrochloride is the most toxic of the compounds studied, and with the exception of the meta-substituted amino-ketones, replacement of chlorine with bromine increases toxicity. More generally a consideration of toxicities shows they are not in the same order as the pressor activities. All the halogen derivatives considered, except those containing a nuclear hydroxyl are more toxic than the parent compounds.

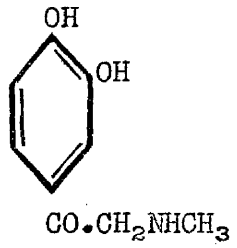
Gurd (69) also studied the same compounds and substantiated the order of pressor activities reported by Edkins and Linnell. In addition they found that all exhibit some sympathomimetic properties on isolated organs, though in certain cases there was some evidence that while small doses produce sympathomimetic effects, larger doses produce opposite effects.

Tainter observed that l-epinephrine is one hundred and eighty-three times as active as β-phenylethylamine (15) and three hundred and sixty-eight times as active as p-chlor-β-phenylethylamine (7). Thus the introduction of chlorine into the para position of β-phenylethylamine decreases its pressor activity in cats by one half. Cocaine almost completely abolishes the pressor action of the chloro compound, and thus it may be classed as a pseudosympathicotropic drug.

The only studies of the effect on physiological properties of the introduction of fluorine into a pressor molecule found in the literature were those reported by Hansen (70) and Suter and Weston (71). The former found that 3-F,4-OH-ω-aminoacetophenone (XX) as well as 3-Cl,4-OH-ω-amino-acetophenone possess vasopressor properties weaker than those of adrenalone (XXI)



(XX)



(XXI)

in anesthetized dogs. Moreover the fluorine compound is slightly less active than the corresponding chlorine analog. Suter and Weston in studying the effect of p-fluorine substitution in β-phenylethylamine, β-phenylisopropylamine, and β-phenylethylmethylamine found that in female white mice (orally) the fluorine compounds were more toxic than the unsubstituted parent molecules. In dogs p-fluoro-β-phenylisopropylamine and β-phenylisopropylamine showed similar pressor activity. Insufficient data were given to compare the pressor activities of the two p-fluorine derivatives with their unsubstituted parents.

OBJECT AND METHOD OF INVESTIGATION

The available studies of the halogen pressor amines, previously summarized, afford some indication of the effect of halogen substitution and position isomerism upon sympathomimetic activity. However it is important to note that these studies were made with incomplete series of compounds in which the various halogens were not present in the same parent molecule. These investigations were also limited by the lack of ortho halogen substituted members. Furthermore, except for p-chlorpropadrine, the compounds investigated were not amino alcohols, which have been shown to be the most active of the sympathomimetic amines. For these reasons it is difficult to draw definite conclusions and satisfactory correlations.

Therefore this investigation was undertaken with the object of making available for future pharmacologic study a series of halogen compounds in which various halogens have been introduced into different positions of the same pressor amine. Propadrine was selected as the parent in which to study halogen substitution since it contains the optimum structures; namely, the aromatic nucleus and primary amino group attached to adjacent carbon atoms, a three carbon side chain which confers oral activity, and an alcoholic hydroxyl on the carbon atom bearing the phenyl group.

In addition, as seen by referring to table 7, since the effects of a number of ring substitutions in the propadrine series have been well established, a further extension of this series by the inclusion of other halogen derivatives would make possible a more complete correlation of the effects of halogen substitution with those of the other substituents.

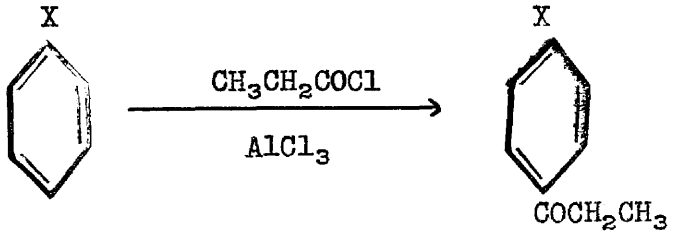
It has been shown that propadrine and a number of its ring substituted derivatives may readily be obtained by a general method, involving nitrosation of the corresponding ketones and subsequent catalytic reduction of the resulting oximino-ketones to the amino-alcohols (20,30,60).

$$Ar.CO.CH_2CH_3 \xrightarrow[HCl]{RONO} AR.COCH(:NOH)CH_3 \xrightarrow[Pd]{(H)} Ar.CHOH.CHNH_2.CH_3$$

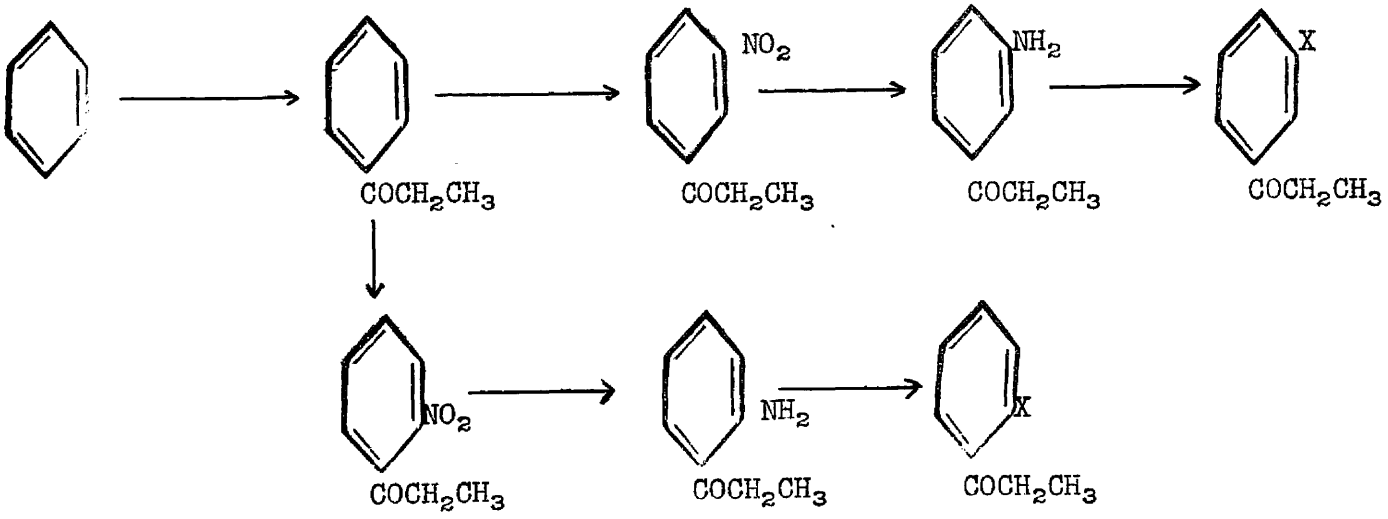
Since both stages of the synthesis give good yields, it was proposed to adopt this scheme in this investigation.

For the necessary intermediate halogen-substituted propiophenones the following series of reactions was planned.

(a) Para halogen ketones (X=F,Cl, and Br)



(b) Ortho and meta halogen ketones (X=F,Cl, and Br)



EXPERIMENTAL

I. General

All temperatures recorded in this investigation are Centigrade degrees and were determined with Anschutz "stem-immersion" thermometers.

Analyses for nitrogen were carried out by the Kjeldahl-Gunning method; analyses for Cl (as HCl) were carried out by the Volhard method.

Volumes of hydrogen recorded in the catalytic reductions are uncorrected.

The semicarbazones of the ketones were prepared by an adaptation of the method of Shriner and Fuson (101). One gram or 1 cc. of the ketone was added to a solution of 1g. of semicarbazide hydrochloride and 1.5g. of sodium acetate in 5 cc. of water in a small flask. Sufficient alcohol was then added, except in the case of m-nitropropiophenone where dioxane was used just to dissolve the ketone. The solution was then heated to the boiling point and allowed to stand in a cool place until the semicarbazone precipitated. The crystals were filtered off and recrystallized from dilute alcohol.

In experiments where compounds were oxidized to their corresponding benzoic acid derivatives in order to verify the position of the halogen in the ring, the oxidations were carried out according to the directions of Shriner and Fuson (102) using potassium permanganate.

Approximately 1g. of compound was added to 80 cc. of water containing 4g. of potassium permanganate. The mixture was heated under reflux for 2 hours, cooled, and carefully acidified with sulfuric acid. The excess manganese dioxide was removed by the addition of sodium bisulphite. The precipitated acid was collected on a filter and dissolved with 10%

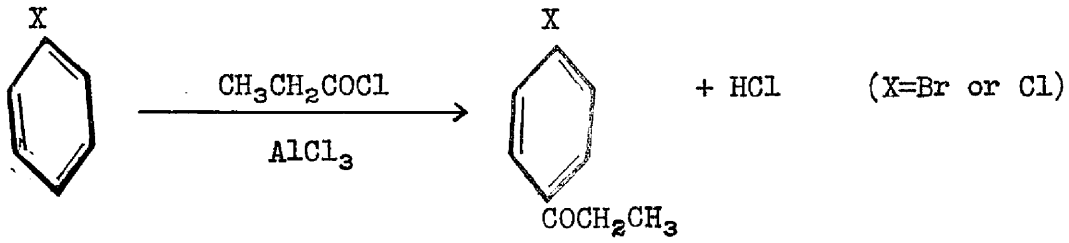
sodium bicarbonate solution on the filter. The acid was reprecipitated by addition of concentrated hydrochloride acid and, unless otherwise specified, was recrystallized from dilute alcohol.

II. Synthesis of Ketones

A. Para Halogen Propiophenones

The following methods are recorded in the literature for the preparation of p-chloro- and p-bromopropiophenone.

(1) Friedel-Crafts Synthesis. Collet (95) prepared these two compounds by the reaction:



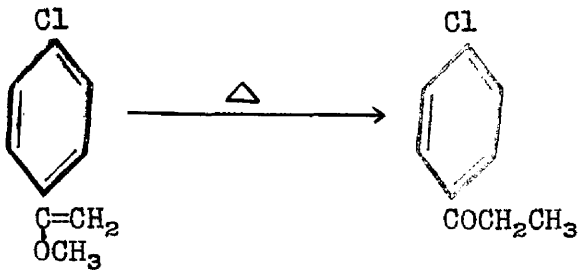
p-Chloropropiophenone was obtained as colorless crystals, melting at 35-36°C. The p-bromo compound melted at 44-5°. No yields were reported by this investigator.

Hartung, Munch and Crossley (20) obtained p-chloropropiophenone in a yield of 81% by reacting propionyl chloride and chlorobenzene in the presence of aluminum chloride. They reported a boiling point of 115° (3mm.) for this compound.

Edkins and Linnell (65) also using the Friedel-Crafts reaction, prepared these two compounds using the conditions described by Adams and Noller (96). Propionic anhydride was gradually added to a hot solution of the appropiate aryl halide in carbon disulphide containing suspended aluminum chloride. The p-chloropropiophenone was obtained as a liquid distilling at 152° (30 mm.) in a yield of 57%. It solidified on strong cooling and on recrystallization from absolute alcohol at -15°, formed fine white needles, m.p. 35.8° (corr.) p-Bromopropiophenone was obtained

in a yield of 56.5%, b.p. 167° (30 mm.). Recrystallized by freezing from alcoholic solution, this ketone occurred in fine white needles, m.p. 47°.

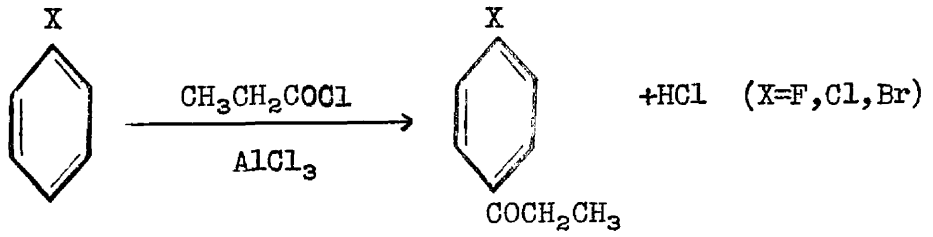
(2) Rearrangement of p-chloro- -methoxystyrene. By heating p-chloro- -methoxystyrene in a sealed tube at 300 , Lauer and Spielman (97) were able to obtain p-chloropropiophenone in a 68% yield according to the reaction:



Their product boiled at 134-7° (31 mm.) and its semicarbazone melted at 175-6°. Although the yield is satisfactory, the preparation of the intermediate styrene derivative requires four reactions.

In this investigation p-fluoro-, p-chloro-, and p-bromopropiophenone were prepared by two adaptations of the Friedel-Crafts reaction.

Procedure 1 consisted of a modification of the method used by Adams and Noller (96) for the preparation of p-chloroacetophenone and involved the following reaction:



In a 2-l. round bottomed, three-neck flask, fitted with a mechanical stirrer, separatory funnel, and reflux condenser connected to a gas absorption trap for disposing of evolved hydrogen chloride gas, was placed 1 mole of the aryl halide and 400 cc. of carbon disulphide which previously

had been dried over anhydrous aluminum chloride. To this mixture was then added 147 g. (1.1 moles) of anhydrous aluminum chloride (E.K. Co). Then 92.5 g. (1 mole) of propionyl chloride was added slowly to the well stirred mixture over a period of about 45 minutes. The addition of the acid chloride was accompanied by a vigorous evolution of hydrogen chloride, refluxing of the carbon disulphide, gradual solution of the suspended aluminum chloride, and the darkening of the reaction mixture from yellow to a dark red-brown. After addition of the acid chloride, gentle refluxing was maintained by a water bath until the evolution of hydrogen chloride had practically ceased (about three hours).

A condenser was attached to one of the side necks and the carbon disulphide distilled off (steam bath). The reaction mixture was cooled to room temperature and the complex decomposed by the addition of an ice-water-hydrochloric acid mixture. Additional concentrated hydrochloric acid was added when necessary to dissolve any remaining aluminum compounds. The dark oil which separated was removed and the aqueous layer extracted with ether. The oil was dissolved in ether extracts which were then washed twice with water, with 10% sodium hydroxide solution until the washings were alkaline, and twice more with water. The ethereal solution was dried over calcium chloride, filtered, and the ether removed by distillation from a water bath. The residue was distilled from a Claisen flask. In the case of p-fluoropiophenone the desired fraction was redistilled while in the cases of p-chloro- and p-bromopropiophenone, the compounds were recrystallized by the gradual addition of cold water to their alcoholic solutions. Physical constants and yields of the three para halogen propiophenones are recorded in table 9.

Procedure 2 consisted of a modification of the above procedure and was employed in an attempt to improve the yields previously obtained. This

aim was accomplished since in all cases previous yields were improved. The modifications introduced consisted primarily of the use of suction to remove more completely the evolved hydrogen chloride, and the decomposition of the product in the presence of solvent to decrease the violence of the decomposition and mechanical loss.

The aryl halide, pripionyl chloride, and aluminum chloride were reacted in carbon disulphide as the solvent in the same proportions, manner, and apparatus described in the preceding procedure. After all the acid chloride had been added, gentle refluxing was maintained on a water bath for about two and one-half hours, at the end of which time the evolution of hydrogen chloride had greatly lessened. The gas absorption trap was removed, the end of the reflux condenser attached to a water pump, and suction applied for an additional hour to remove hydrogen chloride more completely. The suction was adjusted to prevent too vigorous refluxing of the solvent. At this stage the reaction mixture had acquired a dark red brown color.

The reaction flask was surrounded by a cold water bath, and the complex decomposed in the presence of the solvent by the dropwise addition of water from the separatory funnel. Too violent refluxing of the solvent was prevented by regulating the rate of addition of the water, and stirring was continued during the decomposition. When the vigorous evolution of hydrogen chloride had ceased, the decomposition was complete and any suspended aluminum compounds were dissolved by the addition of hydrochloric acid. In order to allow a better separation of the carbon disulphide and aqueous layers, which had become partially emulsified, the reaction mixture was filtered with suction.

After removing the carbon disulphide layer, the aqueous solution was extracted twice with carbon disulphide. The carbon disulphide solutions were combined, washed twice with water, with 10% sodium carbonate solution

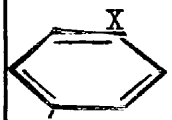
until the washings were alkaline, twice more with water, and dried over calcium chloride. The solution was filtered and the carbon disulphide removed by distillation from a water bath through a short column. The lower boiling fractions were removed by distilling the oily residue at atmospheric pressure, and the desired ketones were distilled at reduced pressures from a Claisen flask.

The yields obtained by this procedure and the melting points of the semicarbazones prepared are also recorded in table 9.

All the ketones by permanganate oxidation produced their corresponding p-halogen benzoic acids, thus verifying the position of the halogen in the ring.

TABLE 9

Para halogen propiophenones

 $COCH_2CH_3$ X=	Appearance	m.p. °C	b.p. °C	% yield Procedure 1	% yield Procedure 2	Semicarb. m.p. °C
F	light yellow oil	-	215-17 (atm.)	63	86	196-7
Cl	colorless needles	34-5	246-50 (atm.) 114-118(2mm.)	51	76	176-7
Br	colorless needles	45-6	137-40 (2mm.)	47	58	170.5-171.5

B. Meta Halogen Propiophenones

Propiophenone

This intermediate was prepared by the Friedel-Crafts reaction. In a typical run 185g. (2 moles) of propionyl chloride was reacted with 800cc. of benzene (the excess benzene serving as the solvent) containing 293 g. (2.2 moles) of anhydrous aluminum chloride according to procedure 2 previously described for the para halogen propiophenones. Distillation of the crude product gave 245g. (yield of 91%) of propiophenone (yellow oil), b.p. 75-8° (2mm.), 216-19° (atm.).

m-Nitropropiophenone -Nitration of propiophenone.

m-Nitropropiophenone had been previously prepared by the nitration of propiophenone.

Hartung and co-workers (30) obtained this compound in yields of 27-50%, m.p. 97° (from 70% alcohol), by adding propiophenone slowly to cold agitated fuming nitric acid below 10° (75 cc. acid/0.1 mole ketone). An oily by-product which they stated to be undoubtly the ortho isomer was also obtained.

Barry (99) reported a melting point of 100° after recrystallization from alcohol for this compound which he obtained by dropping propiophenone on red fuming nitric acid. A syrupy product, probably the ortho isomer, was obtained when warm fuming nitric acid was used.

Elson, Gibson and Johnson (100) ran propiophenone in lots of 30 cc. into 140 cc. of stirred nitric acid (d. 1.5) kept below 0°. After 1/2 hour the product was poured on ice and the crystalline meta compound was separated and recrystallized from alcohol, m.p. 98-100°. From the filtrate, made alkaline and extracted with ether, was obtained o-nitropropiophenone after evaporation of the ether. No yields were reported for this nitration.

In this investigation, preliminary experiments were tried using various nitrating mixtures, such as sulfuric and conc. nitric acids, sulfuric and fuming nitric acids and glacial acetic and fuming nitric acids. However, it was found that the use of fuming nitric acid alone gave the best results. Thus it was decided to use fuming nitric acid (Baker's C.P. grade-d 1.5) for the subsequent preparation of m-nitropropiophenone, as well as the o-isomer. In the first series of experiments with this reagent the reaction temperature was kept below 0° by the addition of solid carbon dioxide chips to the reaction mixture. At these temperatures little or no oxidation products were produced.

In a typical run. 300 cc. of fuming nitric acid was placed in a liter beaker surrounded by an ice-salt-water bath equipped with a mechanical stirrer, dropping funnel, and thermometer. The acid was cooled to -10° by the addition of chips of solid carbon dioxide and 53.6 g. (0.4 moles) of propiophenone was slowly added from the dropping funnel with stirring. Throughout the addition, the temperature was kept between -10° and -5° by the further addition of solid carbon dioxide as required and by regulating the rate of dropping of the propiophenone.

Stirring was continued for 10 minutes after all of the propiophenone was added, and then the reaction mixture was poured over crushed ice. The yellow oily crystals of m-nitropropiophenone which separated were removed by filtration with suction and washed successively with water, 10% sodium carbonate, and again with water on the filter. The crystals were washed finally with a little cold 90% alcohol to remove adhering o-nitropropiophenone. The crude meta isomer was then recrystallized from 95% alcohol. 43g. of slightly yellow crystals melting at 98.5-99° was obtained, a yield of 60%. Semicarbazone - m.p. 188-9°.

The aqueous filtrate and washings were extracted with ether to remove the o-nitropropiophenone which was present as a tan oil, the ether extract dried over calcium chloride and filtered. The ether was removed by distillation from a hot water bath and the crude o-nitropropiophenone (dark oil), together with that obtained by removal of the alcohol from the alcoholic wash, weighed 24 g. (30% yield).

The negligible precipitate produced by acidification of the sodium carbonate wash indicated that the nitration was accompanied by practically no oxidation.

A second series of nitration experiments was undertaken with the object of studying the effect of higher temperatures on the course of nitration, and to obtain if possible higher yields of the ortho isomer which was required as an intermediate in the preparation of the ortho halogen propiophenones. At each temperature studied, two half-mole portions of propiophenone were nitrated in two separate runs and the combined reaction products, representing 1 mole, were isolated and purified together. This procedure of nitrating each mole of propiophenone in two separate runs was adopted since previous experience had shown that temperature control for quantities larger than 0.5 moles was more difficult than for smaller amounts. In addition, when larger quantities are used, the initial portions of propiophenone are required to remain in contact with the nitric acid for longer periods, thereby increasing the tendency for oxidation to take place. The following general procedure was adopted for this nitration study and includes a more efficient method than that previously used for the isolation of the products.

In a three-neck liter flask fitted with a mechanical stirrer, dropping funnel, thermometer and ice bath was placed 425 cc. of fuming nitric acid.

Stirring was started and when the temperature of the acid had dropped to the desired temperature, 67 g. (0.5 moles) of propiophenone was added from the dropping funnel. The temperature of the reaction was maintained within ±2° by adjusting the rate of addition and of external cooling. Stirring was continued for 5 to 10 minutes longer after the complete addition of the propiophenone.

The reaction mixture of two such runs was poured upon 2 l. of ice and water, and the yellow oily crystals which separated was filtered with suction. The aqueous filtrate was extracted with three 200 cc. portions of benzene, the benzene extracts combined, warmed to 60 and used to dissolve the product on the filter. The benzene solution after washing three times with 100 cc. portions of water, with 10% sodium hydroxide until the washings were practically colorless, and finally three times more with 100 cc. portions of water, was dried over calcium chloride and filtered. After removal of the benzene by distillation through a short column, a mixture of the ortho and meta isomers was obtained. The oily o-nitropropiophenone was removed by washing the mixture on a filter with cold 95% alcohol in which the meta isomer is insoluble.

The ortho isomer was obtained as a brown oil after removal of the alcohol by distillation, and was placed in a refrigerator for several days to allow the separation of a small amount of the crystalline meta isomer which had been dissolved by it. The meta compound was filtered off, combined with the other portion, and the total m-nitropropiophenone recrystallized from 95% alcohol, m.p. 98.5-99°.

The sodium hydroxide washings were made acid with conc. hydrochloric acid and the ppt. obtained was washed thoroughly with water, dried over calcium chloride and weighed. This product was soluble in sodium bi-

carbonate solution and was probably a mixture of ortho and meta nitrobenzoic acids.

Table 10 gives the yields of the products produced at the various temperatures of the nitrations.

TABLE 10

Nitration of propiophenone with fuming HNO_3

Nitration temp. °C ± 2	Yields - from 1 mole of propiophenone				
	Recrystallized m-nitropropiophenone		Crude o-nitropropiophenone		Crude NaOH extractive
	g.	%	g.	%	g.
10	92	51.4	67	37.4	4
15	85	47.5	66	36.8	7
20	74	41.3	63	35.2	9
25	64	35.8	61	34.0	16

m-Aminopropiophenone

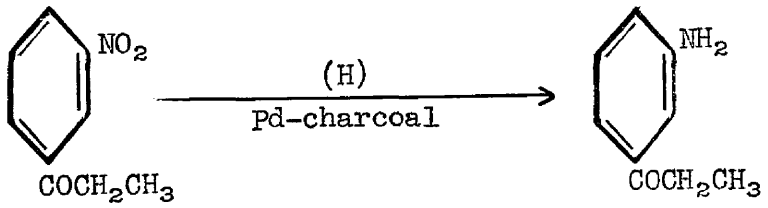
The first preparation of this compound, as its hydrochloride, was reported by Comanducci and Pescitelli (103) who obtained it by the reduction of m-nitropropiophenone with tin and hydrochloric acid at 60°. However their reported melting point of 170° (dec.) for the salt is much lower than reported by subsequent investigators.

Elson, Gibson, and Johnson (100) obtained the free amine by the reduction of m-nitropropiophenone with iron and acetic acid. It was isolated in yields which were variable and as high as 60%, as a pale yellow oil, b.p. 168-9°

(15 mm.) which formed a yellow solid m.p. 42°.

Hartung, Miller, Munch, and Crossley (30) reduced m-nitropropiophenone with tin and hydrochloric acid and obtained the free amine in yields of 63-69%; it distilled at 115-20° (5-7 mm.) and its hydrochloride melted at 202.5°.

Since a number of reports in the literature have shown that the aromatic nitro group can be converted to the primary amine in excellent yields by catalytic hydrogenation (104,105,106,107), this method came under consideration as a possible means of improving the yields of m-aminopropiophenone previously reported. Using a palladium on charcoal catalyst with benzene as the solvent it was found possible to reduce selectively the nitro-group of m-nitropropiophenone to the amine without affecting the ketone group. The use of benzene as the solvent facilitated the isolation of the amine as the hydrochloride from the reaction mixture in a relatively pure state, and may be a factor in preventing the undesired reduction of the ketone group, though this latter possibility was not sufficiently studied. Reductions were carried out both under ordinary pressures and under initial pressures of 300 pounds. The reaction involved is:



(1) Preparation of the catalyst. The palladium-charcoal catalyst was prepared by essentially the same method described by Hartung (60,108). A suspension of 1 g. of palladium chloride crystals or 10 cc. of a solution of palladium chloride (each cc. representing 0.1 g. of palladium chloride) and 10 g. of Norite (E.K. and Co.) in 200 cc. of distilled water was shaken

in an atmosphere of hydrogen until saturated. The catalyst thus obtained was filtered off, washed thoroughly with distilled water, alcohol, and ether, and was kept in a vacuum desiccator over sulphuric acid until used.

(2) Hydrogenations. Three grams of catalyst was added to a solution of 53.7 g. (0.3 moles) of m-nitropropiophenone in 300 cc. of benzene. The mixture was shaken in an atmosphere of hydrogen in an apparatus similar to that described by Hartung (108)— at room temperature and at approximately atmospheric pressure. The theoretical amount of hydrogen required to reduce the nitro-group to the amino-group was absorbed in approximately 13 hours, after which time the absorption of hydrogen ceased.

The reaction mixture was filtered to remove the catalyst, the filtrate placed in a separatory funnel, and the water formed during the reduction was drawn off from the benzene layer. The benzene solution was dried over anhydrous sodium sulphate and filtered. Dry hydrogen chloride gas was passed into the dried benzene solution until no more m-aminopropiophenone hydrochloride was precipitated. The precipitate was collected on a filter, using suction, washed with benzene, then with acetone until the precipitate was colorless, and finally once with ether. m-Aminopropiophenone hydrochloride was thus obtained in yields of 83-88%, m.p. 198-99.5° (dec.). The brown discoloration which the compound often developed on standing in a vacuum desiccator could be removed by recrystallization from a mixture of ethanol and isopropanol (3:1) and charcoal. A larger yield of recrystallized compound was obtained by adding ether to the filtrate.

When the reductions were carried out under initial pressures of 300 lbs., the reduction was complete in approximately two and one-half to three hours. Thus the use of these elevated pressures increased the speed of the reduction about 4 times. In these experiments a pressure hydrogenator bomb (American Instrument Co.) fitted with a glass liner was employed.

The reaction mixture was agitated by a mechanical rocking device, and the hydrogen absorption was followed by observing the fall of pressure on the attached gauge.

It was found possible to use the same catalyst for at least two runs, but its use a third time was not attempted because of the decreased activity of the catalyst during the second run. A reduction using a catalyst previously used once required twice as much time to absorb the theoretical amount of hydrogen as a fresh catalyst.

(3.) Oxime of m-aminopropiophenone. The formation of an oxime by the reduction product verified the presence of the ketone group. The solubility of this oxime in both aqueous acid and base is to be expected of a compound containing both an amino- and oximino group. The following preparation was used.

Two grams of hydroxylamine hydrochloride and 2 g. of m-aminopropiophenone hydrochloride were dissolved in 15 cc. of a saturated solution of sodium bicarbonate. The free amine which separated as an oil was just dissolved by the addition of alcohol. More bicarbonate solution was added in small portions, as well as sufficient alcohol just to keep the amine in solution, until the solution became slightly basic. At this point the oxime precipitated, and was collected on a filter and washed thoroughly with water. After recrystallization from 50% alcohol (charcoal) the oxime was obtained in long colorless needles, m.p. 112-113°.

(4) m-(p-Toluenesulphonamido)-propiophenone. Two grams of m-aminopropiophenone hydrochloride and 2 g. of p-toluenesulphyonyl chloride were shaken with 15 cc. of 10% NaOH until all of the amine went into solution. The solution was filtered, made acid, and the precipitate which formed was collected on a filter and recrystallized several times from dilute alcohol (charcoal). Colorless needles m.p. 102-3° were obtained. Reported m.p. 97°-from alcohol (100).

m-Fluoropropiophenone

A previous report of this compound was not found in the literature. However fluorine can generally be introduced into the aromatic nucleus by replacement of an amino group through diazotization and subsequent decomposition reactions. This general scheme can be carried out in several ways.

(1) Decomposition of a diazopiperidide in the presence of concentrated hydrofluoric acid (109,110).

$$ArN{=}N{-}NC_5H_{10} \xrightarrow{2HF} ArF{+}N_2{+}C_5H_{10}NH{\cdot}HF$$

However the reaction is violent and cannot be conveniently used with quantities greater than 10-15 g. of piperidide.

(2) Decomposition of a diazonium chloride in the presence of conc. hydrofluoric acid (111).

(3) Diazotization of the aromatic amine and warming of the resulting diazonium compound in the presence of excess hydrofluoric acid (112).

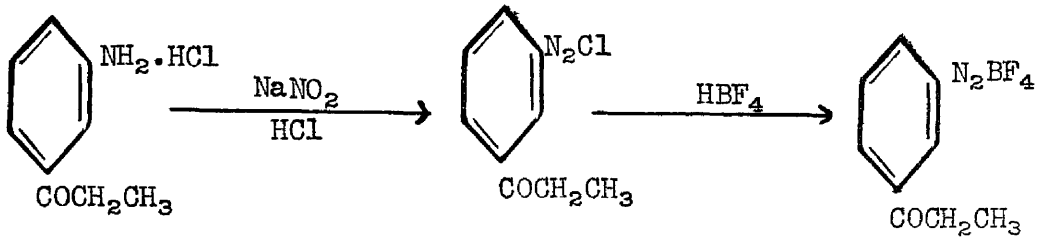
(4) Heat decomposition of a diazonium borofluoride (113,114).

$$ArN_2BF_4 \xrightarrow{\Delta} ArF{+}N_2{+}BF_3$$

The first diazonium borofluorides were prepared by Wilke-Dorfurt and Balz (115,116) who found them to be stable, insoluble salts. Balz and Schiemann (113) found that these compounds could be decomposed quietly and smoothly by heat with the production of the aromatic fluorine compound. This method has several advantages over the others. It has a widespread applicability, produces good yields, requires no special apparatus, and the intermediate borofluorides are stable and can be easily prepared and isolated.

Because of its advantages as a laboratory procedure, the diazonium borofluoride method was used in this work to prepare m-fluoropropiophenone.

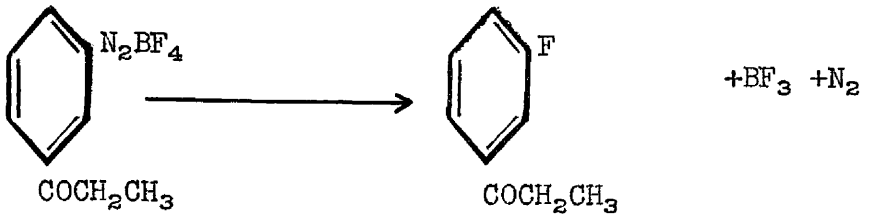
The intermediate diazonium borofluoride was prepared by a method similar to that proposed by Balz and Schiemann (113), according to the reactions:



A solution of 83.5g. (0.45 moles) of m-aminopropiophenone hydrochloride in 45 cc. of hydrochloric acid (d 1.19) and 200 cc. of water was placed in a 500 cc. beaker surrounded by an ice-salt-water bath, and fitted with a mechanical stirrer, thermometer, and dropping funnel. The solution was cooled to 0-5° and some of the salt crystallized from the solution; however as diazotization proceeded, the salt gradually redissolved. While stirring vigorously, a solution of 34.5 g. (0.5 moles) of sodium nitrite in 60 cc. of water was added slowly from the dropping funnel, keeping the temperature of the mixture at 0-5°. When the diazotization was complete, a cold filtered solution of 120 cc. of 48% borofluoric acid was rapidly added to the diazonium solution and stirring was continued for 15 min. longer. The solid which separated was collected on a filter, using suction, and washed twice with cold alcohol, thoroughly with ether, and partially dried by drawing air through it. The resulting pinkish solid was dried overnight in a vacuum desiccator over conc. sulphuric acid. The diazonium borofluoride was thus obtained in a yield of 98 g. (88%) and decomposed at 97-8°.

Initial experiments carried out for the thermal decomposition of the dry diazonium borofluoride by an adaptation of the method described by Flood (117) proved unsatisfactory in that a large amount of tar was formed and the yields of m-fluoropropiophenone were very small. However it was subsequently found that satisfactory yields of m-fluoropropiophenone could be obtained

if the decomposition was carried out in the presence of an inert hydrocarbon solvent. Toluene was selected as the solvent since its boiling point is somewhat higher than the decomposition point of the borofluoride. The decomposition proceeded according to the reaction:



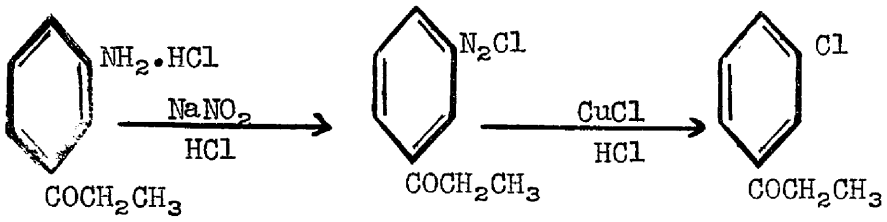
The procedure used is as follows:

Toluene (350 cc.) was heated to its boiling point in a liter 3 neck flask fitted with a mechanical stirrer and a reflux condenser connected to a gas absorption trap for the evolved boron trifluoride. The stirrer was set in motion and 98 g. (.395 moles) of the diazonium borofluoride was added in 1 to 2 g. portions through one of the necks to the toluene kept just below its boiling point; each portion was added after the preceeding one had been decomposed. Toward the end of the decomposition some tar which had formed separated from the toluene solution.

After the decomposition was complete, the toluene solution was cooled to room temperature and washed three times with water, three times with 5% sodium hydroxide solution, and finally twice with water. After drying over calcium chloride, the solution was filtered and the toluene removed by distillation through a short column. The residue was fractionated under reduced pressure and the m-fluoropropiophenone was obtained in a yield of 40 g. (67.8%) as a slightly yellow oil, b.p. 94-96° (4-5 mm.) which formed colorless crystals when cooled in an ice bath. Its semicarbazone melted at 187.5-188°. Oxidation with permanganate produced m-fluorobenzoic acid.

m-Chloropropiophenone

This compound was not found described in the literature. It was prepared by the Sandmeyer reaction by a procedure patterned after that described by Marvel and McElvain (118).



The cuprous chloride— hydrochloric acid solution required for the reaction was prepared by adding, with stirring a solution of 33.3 g.(0.175moles) of sodium meta sulphite and 40 g. (1 mole) of sodium hydroxide in 300 cc. of water to a warm solution of 162.3 g. (0.65 moles) of crystallized copper sulphate and 76 g. (1.3 moles) of sodium chloride in 500 cc. of water over a period of five to ten minutes. The mixture was allowed to cool to room temperature and the cuprous chloride, which separated as a white powder, was washed thoroughly by decantation and dissolved in a mixture of 200 cc. of hydrochloric acid (d 1.19) and 150 cc. of water.

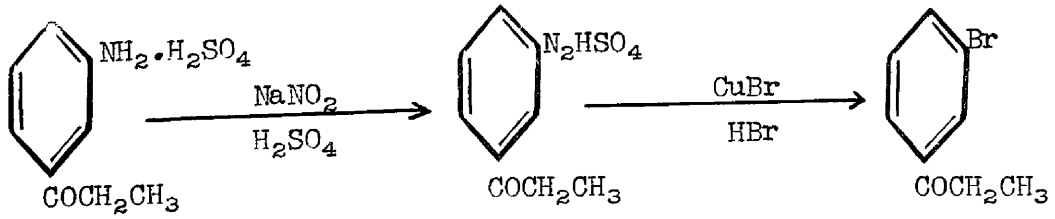
Immediately following the preparation of the above solution, 92.7 g. (0.5 moles) of m-aminopropiophenone hydrochloride in 300 cc. of water and 200 cc. of hydrochloric acid (d 1.19) was diazotized in a liter beaker by the addition of a solution of 34.5 g. (0.5 moles) of sodium nitrite in 75 cc. of water. The temperature of the mixture was kept at 0-5° throughout the reaction by an ice-salt-water bath. The cold diazonium solution was then poured rapidly into the stirred cuprous chloride-hydrochloric acid solution, and the resulting mixture became thick due to the separation of a solid complex. The cold mixture was then allowed to warm up to room temperature, during which time the complex began to break down with the evolution of nitrogen. The decomposition was completed by heating the mixture to 70°, stirring being

continued, and maintaining the temperature until the evolution of nitrogen ceased (1/2 - 1 hr.). The orange crystalline solid which separated on cooling the mixture was filtered off and dissolved in 200 cc. of benzene which had been previously used to extract the filtrate. The benzene solution was washed with water, with 5% sodium hydroxide solution, and again with water. The benzene was removed by distillation and the residue distilled with steam. The distillate containing the yellow, solid m-chloropropiophenone was extracted with benzene, and the benzene solution washed with water, dried over calcium chloride, and filtered. The yellow solid, obtained after distilling off the benzene, was dissolved in 200 cc. of 95% alcohol and the alcoholic solution was decolorized with charcoal. Water (75 - 100 cc.) was added to the filtered alcoholic solution which was then placed in a refrigerator over night to complete the crystallization of the m-chloropropiophenone. A yield of 61 g. (72.4%) of colorless crystals, m.p. 45-46° was thus obtained. Semicarbazone, m.p. 179.5-180°. Permanganate oxidation of this ketone produced m-chlorobenzoic acid.

m-Bromopropiophenone

This ketone has been described by Elson, Gibson, and Johnson (100). They obtained it from m-aminopropiophenone by a Sandmeyer reaction as a pale yellow solid, m.p. 36°, in a yield of 52%.

In this work it was also prepared by the Sandmeyer reaction from m-aminopropiophenone. The reactions for its preparation are:



The cuprous bromide-hydrobromic acid solution used in the reaction was prepared from 33.3 g. (0.175 moles) sodium meta sulphite, 40 g. (1 mole) of sodium hydroxide, 162.3 g. (0.65 moles) of crystallized copper sulphate, and 72 g. (0.7 moles) of sodium bromide by the method described for cuprous chloride. The cuprous bromide, obtained as a white powder, was washed thoroughly with distilled water by decantation and dissolved in 200 cc. of hydrobromic acid (48%) and 100 cc. of water.

Then 0.5 moles of m-aminopropiophenone hydrochloride was neutralized with 20% sodium hydroxide solution, the free amine separated, washed with water, and dissolved in 84 cc. of conc. sulphuric acid and 350 cc. of water. After diazotizing with a solution of 0.5 moles of sodium nitrite in 75 cc. of water, keeping the temperature at 0-5°, the diazonium solution was added to the cuprous bromide solution, the complex decomposed, and the m-bromopropiophenone isolated and purified as described for the m-chloro-compound. m-Bromopropiophenone was obtained as colorless crystals, m.p. 37.5-40° in a yield of 47 g. (44%). Semicarbazone m.p. 182° reported m.p. 180° (100). Permanganate oxidation of the ketone produced m-bromobenzoic acid.

C. Ortho Halogen Propiophenones

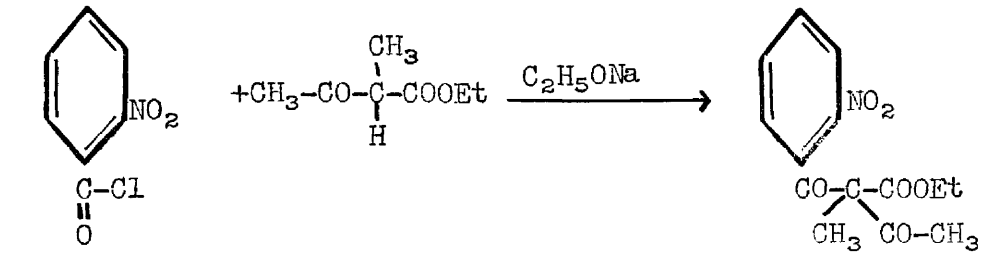
o-Nitropropiophenone

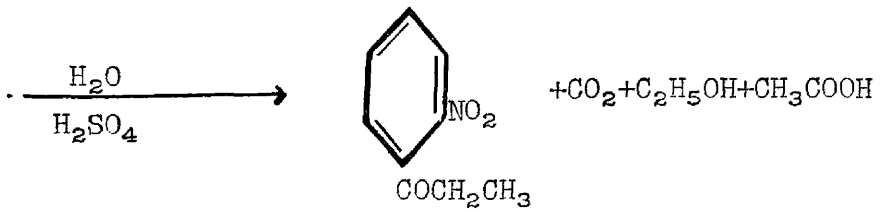
This compound was erroneously reported by Comanducci and Pescitelli (103) as a crystalline compound, m.p. 85°, obtained by adding propiophenone to 136% nitric acid at 40°. However, subsequent workers have shown that the compound is an oil. Moreover, during the present investigation the results of Hartung and Gibson (unpublished) were confirmed; namely, that if the reaction between propiophenone and nitric acid (d 1.5) is allowed to take place above 25-35°, the reaction becomes extremely vigorous and

uncontrollable, brown fumes are evolved and only m-nitrobenzoic is isolated. Additionally, Comanducci and Pescitelli give no proof for the structure of their compound.

Hartung and co-workers (30), and Elson, Gibson, and Johnson (100) obtained it as a side product in the nitration of propiophenone. The former described it as an oil, b.p. 153-60° (7-10 mm.)

Wohnlich (119) and later Auwers and Duesberg (120) prepared this ketone according to the following reactions:





Wohnlich described the compound as a yellow, thick oil with an aromatic odor b.p. 175° (25 mm.)-- yield 42-46%. The latter two investigators obtained it in a yield of 40% as a yellow, thick oil which darkened in the air, b.p. 166-7° (15mm.), 161° (10-11 mm.).

In this work, o-nitropropiophenone was prepared, along with m-nitropropiophenone, by the nitration of propiophenone with fuming nitric acid as described above. The crude ketone after fractionating under reduced pressure was obtained as a yellow oil, b.p. 152-5° (2-3 mm.) which darkened on standing. From 69 g. of crude compound was obtained 54 g. of distilled o-nitropropiophenone. Semicarb., m.p. 183-4°; reported m.p. 182-3° (120).

o-Aminopropiophenone

Comanducci and Pescitelli (103) reduced their purported o-nitropropiophenone with tin and hydrochloric acid and obtained an amine of which the hydrochloride decomposed without melting at about 200°. However, since they obviously did not have o-nitropropiophenone, they could not have had o-aminopropiophenone.

Wohnlich (119) by the reduction of o-nitropropiophenone with tin and conc. hydrochloric acid obtained the free amine as yellowish leaflets, m.p. 45-6° after recrystallization from petroleum ether.

Auwers and Duesberg (120) reduced o-nitropropiophenone with stannous chloride and conc. hydrochloric acid and obtained the free amine as light yellow leaflets, m.p. 46-7° in a yield of 70%.

Elson, Gibson, and Johnson (100) reduced the crude o-nitropropiophenone, which they obtained from the nitration of propiophenone, with tin and hydrochloric acid. The resulting amine was isolated by steam distillation and crystallized from the distillate in pale yellow plates, m.p. 46°.

In this work, o-aminopropiophenone was prepared by the catalytic hydrogenation of o-nitropropiophenone, as described under m-aminopropiophenone, in benzene and using a palladium--charcoal catalyst.

To a solution of 53.7 g. (0.3 moles) of o-nitropropiophenone in 100cc. of benzene was added 5 g. of the catalyst, already described, and the mixture hydrogenated in the bomb hydrogenator at an initial pressure of 300 pounds. Before shaking was started, medium heat was applied for ten minutes. The theoretical quantity of hydrogen was absorbed in approximately seven hours after which time absorption ceased. The reaction mixture was filtered to remove the catalyst, the water formed in the reduction removed, and 300 cc. of benzene added to the filtrate which was then dried over anhydrous sodium sulphate. The amine was isolated as the hydrochloride

salt by the procedure described for m-aminopropiophenone hydrochloride. o-Aminopropiophenone hydrochloride was thus obtained as a pink solid m.p. 184-5° (dec.) in a yield of 73-79%. The salt darkened on standing.

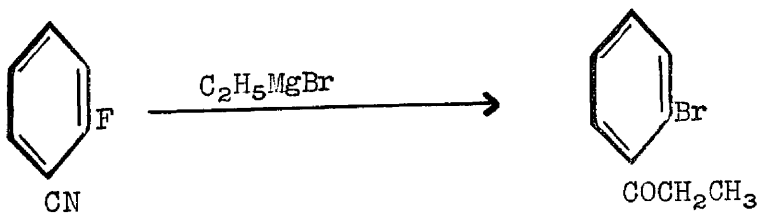
It was found that a higher melting product could be obtained by the following recrystallization. Ten grams of the amine hydrochloride was dissolved in a boiling mixture of 125 cc. of isopropyl alcohol and 50 cc. of ethanol and decolorized with charcoal. After cooling in the refrigerator, 6 g. of slightly tan crystals were obtained which began to darken at about 175 and melted with decomposition at 187-88°. By the addition of ether to the mother liquor 3 g. more of the salt was obtained. However, for the purpose of this investigation, this recrystallization was not necessary.

The following derivatives were also prepared and recrystallized from dilute alcohol.

	m.p. - Found	m.p. - Reported (120)
Benzoyl	131-2°	130°
Oxime[1]	87.5-88°	88-9°
Free Amine	44-5°	46-7°

o-Fluoropropiophenone

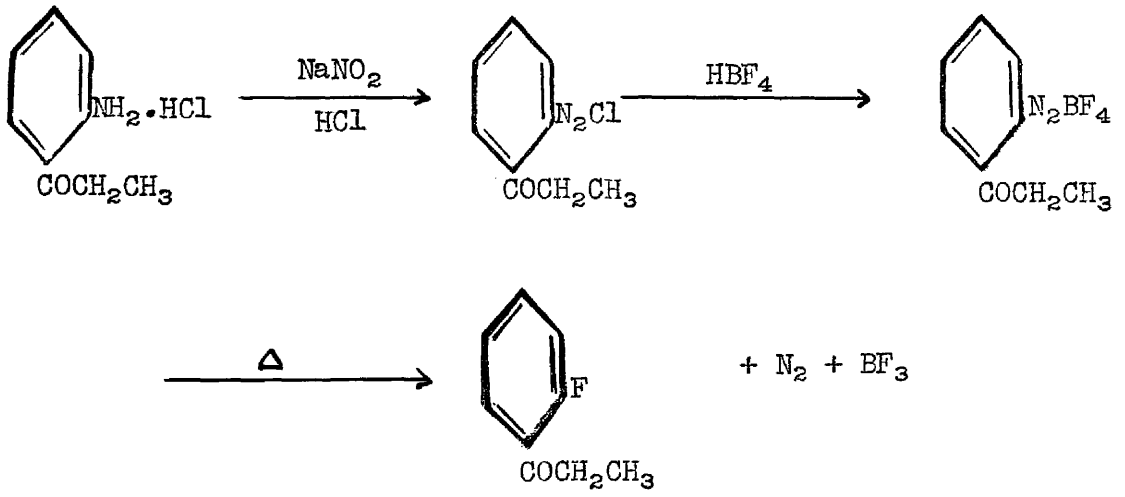
Borsche and Wagner-Roemmich (121) prepared this ketone by a Grignard reaction.



[1]The oxime was prepared by the method described for the oxime of m-aminopropiophenone; it was sol. in aqueous acid and base.

Their product was obtained in a yield of 70% as a colorless oil which did not solidify, b.p. 95-9° (19 mm.).

In this work o-fluoropropiophenone was prepared by decomposition of the diazonium borofluoride, prepared from o-aminopropiophenone hydrochloride, in the presence of a hydrocarbon solvent according to the reaction.

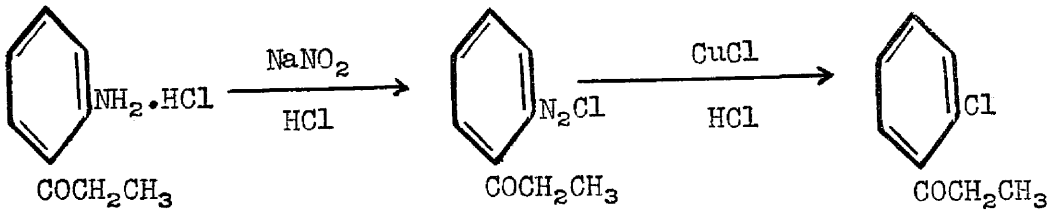


o-Aminopropiophenone hydrochloride (0.3 moles) in 25 cc. of hydrochloric acid (d 1.19) and 100 cc. of water was diazotized at 0-5° by the addition of a solution of 0.3 moles of sodium nitrite in 50 cc. of water. To the cold diazonium solution was then added 70 cc. of borofluoric acid (42%) with stirring. No precipitate formed immediately as in the case of the meta compound, but after standing in the ice bath for 5-10 minutes, the diazonium borofluoride precipitated as a tan powder. After filtering off this salt with suction, a second batch of the diazonium salt was obtained by saturating the filtrate with sodium borofluoride. The total yield of diazonium borofluoride was washed on the filter once with isopropyl alcohol and then thoroughly with ether. After drying in a vacuum desiccator over conc. sulphuric acid, 59 g. (79%) of a light tan powder was obtained, dec. 81-82°.

The diazonium borofluoride (59 g.) was decomposed by dropping the dry powder into 350 cc. of heptane, kept just below its boiling point as described for the decomposition of the diazonium borofluoride prepared from m-aminopropiophenone. The crude o-fluoropropiophenone was fractionated under reduced pressure, and the fraction distilling at 12-13 mm. collected o-Fluoropropiophenone was thus obtained as a yellow oil which did not solidify on cooling, b.p. 87-91° (12-B mm.), in a yield of 17 g. (47%). Semicarbazone, m.p. 143-4°. Permanganate oxidation produced o-fluorobenzoic acid.

o-Chloropropiophenone

A description of this compound was not found in the literature. It was prepared by the Sandmeyer reaction using the procedure described for m-chloropropiophenone.



A solution of 55.6 g. (0.3 moles) of o-aminopropiophenone hydrochloride in 200 cc. of water and 125 cc. of conc. hydrochloric acid was diazotized at 0-5° by the addition of 0.3 moles of sodium nitrite in 50 cc. of water. This cold diazonium solution was added to a cold solution of 0.4 moles cuprous chloride (prepared by the method already described) in 140 cc. of conc. hydrochloric acid and 100 cc. of water. The mixture was allowed to stand for 15 minutes and heated at 70° with stirring for about one hour. The mixture containing the o-chloropropiophenone (dark oil) was extracted with benzene, the benzene extracts washed twice with water, twice with 5% sodium hydroxide, again several times with water, dried over calcium chloride, and

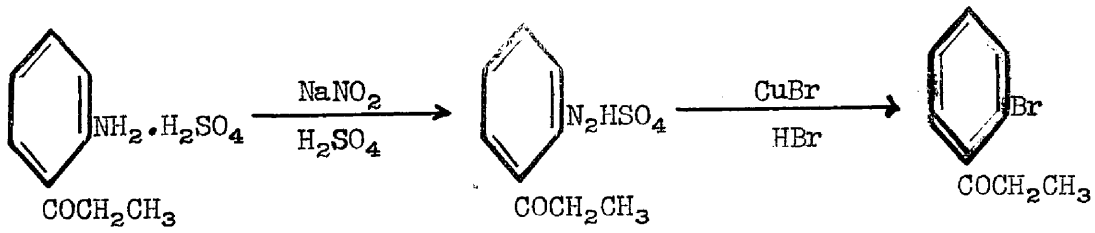
filtered. After removal of the benzene by distillation, the residue was distilled under reduced pressure and the fraction distilling at 104-9 (12 mm.) collected. On redistillation, o-chloropropiophenone was obtained as a yellow oil which did not solidify on cooling, b.p. 105-6° (12 mm.) in a yield of 43 g. (85%). Semicarbazone, m.p. 172-3°. Permanganate oxication produced o-chlorobenzoic acid.

o-Bromopropiophenone

Elson, Gibson, and Johnson (100) prepared this ketone by a Sandmeyer reaction. They obtained it as a pale yellow liquid, b.p. 125° (12 mm.), which did not solidify above -16°, in a yield of 75%.

Borsche and Scriba (122) obtained a 90% yield of this ketone by the Grignard reaction using o-bromobenzonitrile and ethyl magnesium bromide. Their product was a yellowish oil, b.p. 135-40° (16 mm.).

In this investigation, o-bromopropiophenone was prepared by the Sandmeyer reaction using the procedure described for m-bromopropiophenone.



o-Aminopropiophenone hydrochloride (0.3 moles-55.6 g.) was neutralized with 20% sodium hydroxide and the free amine separated and washed with water. A solution of the amine in 50 cc. of conc. sulphuric acid and 200 cc. of water was diazotized at 0-5° by the addition of a solution of 0.3 moles of sodium nitrite in 50 cc. of water. The cold diazonium solution was added to a cold solution of 0.4 moles of cuprous bromide (prepared by the method described under m-bromopropiophenone) in 175 cc. of 48% hydrobromic acid.

The mixture, containing the brown gummy complex, was allowed to stand 15 minutes and heated at 60-70° for about one hour. The o-bromopropiophenone was extracted from the mixture with benzene, the benzene extracts washed twice with water, twice with 5% sodium hydroxide, again twice with water, dried over calcium chloride, and filtered. After removal of the benzene by distillation, the residue was distilled under reduced pressure and the fraction distilling at 116-20° (10-11 mm.) collected. In redistillation, o-bromopropiophenone was obtained as a pale yellow oil which did not solidify on cooling, b.p. 116-18° (10-11 mm.) in a yield of 49 g. (76.6%). Semicarbazone, m.p. 178-9°; reported m.p. 182° (100). Permanganate oxidation produced o-bromobenzoic acid.

III. Nitrosation of the Ketones

The general nitrosation reaction applied to ketones of the type, $Ar.CO.CH_2R$, where R is a methyl or an alkyl group, producing oximinoketones according to the equation

$$Ar.CO.CH_2R \xrightarrow[HCl]{RONO} Ar.CO.CH(:NOH)R$$

was first described by Claisen and Manasse (123). Later studies by Slater (124) and Hartung and his associates (20,30,33,60) further showed that the oximinoketones could be successfully prepared in good yields by this scheme. This general nitrosation reaction was applied to the halogen propiophenones in this investigation.

Only two of the oximino ketones prepared in this work, namely, p-chloro and p-bromo-α-oximinoprophenone, have been previously described in the literature (20,65).

n-Butyl Nitrite

This ester, used as the nitrosating agent, was prepared by the method of Noyes (125) somewhat modified, according to the reaction:

$$2C_4H_9OH+2NaONO+H_2SO_4 \longrightarrow 2C_4H_9ONO+Na_2SO_4+2H_2O$$

A 3 liter, 3-neck flask was fitted with a strong mechanical stirrer, a thermometer, and a dropping funnel leading to the bottom of the flask. Sodium nitrite (380 g. - 5.5 moles) was placed in the flask and 500 cc. of water and 1 Kg. of crushed ice were added. An ice-salt bath provided external cooling. Then 100 cc. of water, 136 cc. of conc. sulphuric acid (d 1.84) and 457 cc. (5 moles) of n-butyl alcohol were carefully mixed and cooled to 0°. This solution was then introduced below the surface of the

nitrite wolution with stirring. Ice was added from time to time, as necessary, to keep the mixture cold. Such addition of ice directly to the reaction mixture decreased considerably the time required for the completion of the reaction. The yellow nitrite which separated was removed, and the aqueous salt solution, to which water was added, was allowed to stand for about 1/2 hour. Any nitrite which further separated was combined with the previous portion. The total yield of ester was washed twice with 50 cc. portions of a solution of 2 g. of sodium bicarbonate and 25 g. of sodium chloride in 100 cc. of water, once with 50 cc. of water, dried over anhydrous sodium sulphate, and filtered. The ester was distilled through a short column and the fraction boiling at 75-78° (atm.) was collected. n-Butyl nitrite was thus obtained as a yellow liquid in a yield of 402 g. (78%).

The nitrite was stored in a glass stoppered bottle in a refrigerator, and when it was more than 2 or 3 weeks old, it was redistilled before using.

General Nitrosation Procedure

The general procedure adopted for the preparation of the nine oximino-ketones obtained in this work by the reaction

$$Ar.CO.CH_2.CH_3 \xrightarrow[HCl]{BuONO} Ar.CO.CH(:NOH)CH_3$$

was similar to that used by Levin (126) and is as follows:

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 was placed the halogen propiophenone dissolved in ether. The stirrer was set in motion and dry hydrogen chloride gas (generated by allowing conc. sulphuric acid to drop on conc. hydrochloric acid) was bubbled through the ether solution at the rate of about 2-4 bubbles per second; stirring and

addition of acid was continued throughout the reaction. After the ether solution was saturated with hydrogen chloride (5-10 minutes), freshly distilled n-butyl nitrite was added by means of the dropping funnel in 0.5-1.0 cc. portions. After addition of the first portion the reaction mixture became orange brown, and after several minutes, a pale yellow; these color changes occurred after the addition of each subsequent portion of nitrite. After the addition of the last several portions, the orange brown color remained. During the reaction the mixture gradually warmed up and the ether refluxed gently. After all of the nitrite had been added, stirring and the addition of the hydrogen chloride were continued for another 15 minutes.

The ether was removed by distillation from a water bath. When practically all the ether was gone, distillation was continued under reduced pressure to remove as completely as possible the butyl alcohol formed in the reaction. The crystalline oximino-ketone obtained was allowed to stand overnight in a vacuum desiccator over conc. sulphuric acid, and the crude product was then recrystallized from a suitable solvent.

n-Butyl nitrite was selected as the nitrosating agent in these experiments since it is more conveniently handled and less likely to be carried out of the reaction mixture by the hydrogen chloride than the more volatile nitrites. It was also chosen in preference to higher boiling nitrites, such as amyl nitrite since n-butyl alcohol formed during the reaction is more easily removed from the reaction product than the higher boiling amyl alcohol.

Ether, by virtue of its ready availability, low boiling point, and desirable solvent properties was found to be a very satisfactory nitrosating medium.

p-Fluoro-α-oximinopropiophenone

p-Fluoropropiophenone was nitrosated by the above general procedure

using 45.6 g. (0.3 M) of the ketone in 300 cc. of ether and 34 g. (0.33 moles) of butyl nitrite (added over 45 min.). The crude yellow crystalline oximino-ketone was recrystallized from toluene and yielded 39 g. of colorless crystals. By extracting the mother liquor with 5% sodium hydroxide, acidifying the extracts with hydrochloric acid, washing the precipitate with water and recrystallizing from dilute alcohol (charcoal) an additional 9 g. of compound was obtained. Total yield of p-fluoro-α-oximinopropiophenone — 48 g. (88.4%), m.p. 106.5-7.5°. Nitrogen found— 7.70, 7.76%; calculated for $C_9H_8FNO_2$— 7.74%.

p-Chloro-α-oximinopropiophenone

Edkins and Linnell (65) attempted unsuccessfully to prepare this compound by adding a solution of butyl nitrite in alcohol and ether to a cold mixture of p-chloropropiophenone and sodium in absolute alcohol. The product which they isolated proved to be p-chlorobenzoic acid. However, they were able to obtain the desired compound by treating a solution of p-chloropropiophenone, in ether, saturated with hydrogen chloride, with butyl nitrite. Their product was isolated as fine white needles from dilute alcohol - m.p. 114°.

Hartung and co-workers (20) also obtained this oximinoketone by the nitrosation of p-chloropropiophenone in ether with butyl nitrite in a yield of 83%, m.p. 122-3°.

In this work, from 50.5 g. (0.3 moles) of p-chloropropiophenone in 300 cc. of ether and 34 g. (0.33 moles) of n-butyl nitrite (added over approx. 45 minutes) was obtained by the general procedure, after recrystallization from 200 cc. of toluene, 47 g. of colorless crystals. An additional 6 g. of compound was obtained from the toluene mother liquor as described for the p-fluoro-compound. Total yield of p-chloro-α- oximinopropiophenone

53 g. (89.4%), m.p. 119-20°. Nitrogen found -- 7.02,7.09%; calculated for $C_9H_8ClNO_2$ - 7.00%.

p-Bromo-α-oximinopropiophenone

Edkins and Linnell (65) in their attempt to obtain this compound by nitrosating p-bromopropiophenone in alcohol, containing sodium, with butyl nitrite obtained only p-bromo-benzoic acid; in ether (saturated with hydrogen chloride) with butyl nitrite, they successfully obtained the oximino-ketone as yellow-brown crystals from alcohol, m.p. 133.6°, in a yield of 82.5%.

In this work, from 63.9 g. (0.3 moles) of p-bromopropiophenone in 300 cc. of ether and 34 g. (0.33 moles) of n-butyl nitrite (added over approx. 45 minutes, was obtained by the general procedure, after recrystallization from 225 cc. of toluene, 52 g. of colorless crystals. The mother liquor treated as described under the p-fluoro-compound yielded an additional 11 g. of compound. Total yield 63 g. (86.8%), m.p. 132-33°. Nitrogen found -- 5.61, 5.88%; calculated for $C_9H_8BrNO_2$-5.79%.

m-Fluoro-α-oximinopropiophenone

The crude yellow crystals obtained from 30.5 g. (0.2 moles) of m-fluoro-propiophenone in 300 cc. of ether and 22.7 g. (0.22 moles) of n-butyl nitrite (added over approx. 35-45 min.) was dissolved in 100 cc. of hot alcohol and decolorized with charcoal. From this alcoholic solution, after the addition of 130 cc. of water and cooling in a refrigerator, was obtained 29g. of of colorless crystals. An additional 2 g. was obtained by concentrating the mother liquor and recrystallizing the resulting crystals from benzene. Total yield 31 g. (85.6%). Nitrogen found -- 73.6, 7.64%; calculated for $C_9H_8FNO_2$-7.74%. m.p. -109-110°.

m-Chloro-α-oximinopropiophenone

The crude yellow product obtained from 50.5 g. (0.3 moles) of m-chloro-

propiophenone in 300 cc. of ether and 34g. (0.33 moles) of n-butyl nitrite (added over approx. 50 min.) was dissolved in 200 cc. of hot toluene and decolorized with charcoal. After concentrating the solution to about 2/3 its original volume and cooling in a refrigerator, 44 g. of colorless crystals were obtained. An additional 5 g. of compound was obtained by concentrating the mother liquor, and recrystallizing the crystals obtained from dilute alcohol (charcoal). Total yield 49 g. (82.7%), m.p. 94-94.5°. Nitrogen found -- 6.93, 6.94%; calculated for $C_9H_8ClNO_2$ -- 7.00%.

m-Bromo-α-oximinopropiophenone

The yellow, crude product from 42 g. (0.2 moles) of m-bromopropiophenone in 300 cc. of ether and 22.7 g. (0.22 moles) of n-butyl nitrite (added over approx. 45-55 min.) was dissolved in 150 cc. of toluene and decolorized with charcoal. After concentrating the solution to 2/3 its original volume and cooling in a refrigerator, 31 g. of colorless crystals were obtained. On concentrating the filtrate further and recrystallizing the resulting crystals from 50% alcohol (charcoal), 6 g. more of compound was obtained. Total yield 37 g. (76.4%), m.p. 104.5-5°. Nitrogen found -- 5.71, 5.78%; calculated for $C_9H_8BrNO_2$ -- 5.79%.

o-Fluoro-α-oximinopropiophenone

The crude product obtained by the general procedure from 13.0 g. (0.09 moles) of o-fluoropropiophenone in 100 cc. of ether and 10.3 g. (0.1 moles) of n-butyl nitrite (added over 15-20 min.) was recrystallized from heptane. A yield of 12 g. (73.6%) of slightly tan crystals, m.p. 82-82.5°, was obtained. Nitrogen found -- 7.71, 7.53%; calculated for $C_9H_8FNO_2$-7.74%.

o-Chloro-α-oximinopropiophenone

The crude product obtained by the general procedure from 33.9 g. (0.2 moles) of o-chloropropiophenone in 200 cc. of ether and 20.6 g. (0.2 moles)

of n-butyl nitrite (added over approx. 30 min.) was recrystallized from heptane. A yield of 30 g. (76%) of colorless crystals, m.p. 102.5-103°, was obtained. Nitrogen found 7.05, 6.87%; calculated for $C_9H_8ClNO_2$ — 7.00%.

o-Bromo-α-oximinopropiophenone

The crude product obtained by the general procedure from 38.3 g. (0.18 moles) of o-bromopropiophenone in 200 cc. of ether and 20.6 g. (0.2 moles) of n-butyl nitrite (added over approx. 30 min.) was recrystallized from heptane. A yield of 31 g. (71.1%) of colorless crystals, m.p. 101-101.5°, was obtained. Nitrogen found - 5.71, 5.72%; calculated for $C_9H_8BrNO_2$-5.79%.

IV. Catalytic Reduction of the Oximino-Ketones

The final phase of this investigation had as its object the reduction of the intermediate oximino-ketones to their corresponding primary amino-alcohols (propadrines).

$$Ar.CO.C(:NOH)CH_3 \xrightarrow{(H)} Ar.CHOH.CHNH_2.CH_3$$

Prior to the work of Rosenmund and Pfankuch (127), the catalytic reduction of oximes invariably resulted in a mixture of primary and secondary amines, with the latter sometimes predominating (128). The production of the secondary bases may be explained by the side reactions (129):

$$R_2C{=}NOH \xrightarrow{(H)} R_2C{=}NH \xrightarrow{R_2CHNH_2} R_2\underset{NH_2}{C}HNHCHR_2 \xrightarrow{(H)} \begin{matrix} R_2CH \\ R_2CH \end{matrix}\!\!>\!NH + NH_3$$

These workers (R. and P.) were the first to prevent the formation of secondary amine by their use of the oxime acetate (benzaldoxime acetate).

In a further study of this problem Hartung (108) was able to reduce benzaldoxime, with a palladinized-charcoal catalyst in absolute alcohol, to the primary amine without contaimination from the secondary base, by the use of three equivalents of hydrogen chloride in the reduction mixture.

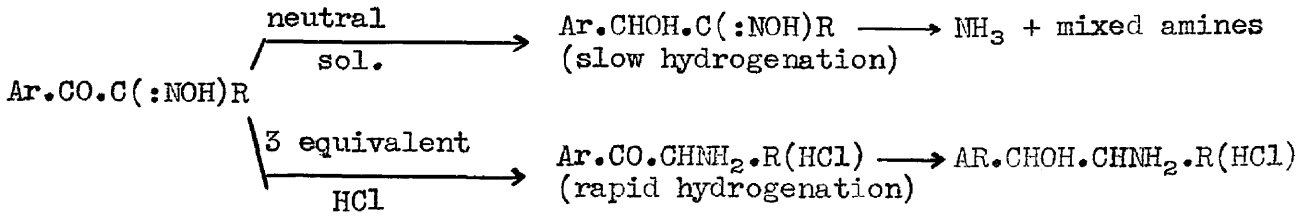
Applying these conditions to a series of oximino-ketones of the type Ar.CO.C(:NOH)R, where R=alkyl, Hartung and his associates (20,30,33,60) prepared the corresponding amino-alcohols in good yields.

$$Ar.CO.C(:NOH)R + H_2 \xrightarrow[(3HCl)]{Pd\text{-}charcoal} Ar.CHOH.CHNH_2.R(HCl)$$

A summary of their studies (130) indicate that:

(1) Reduction of oximino-ketones in absolute alcoholic solution

with a Pd-charcoal catalyst may follow one of two courses:



(2) In the acid solution, reduction of oximino-ketones in which the aromatic portion is a hydrocarbon radical (i.e., phenyl, tolyl, naphthyl) goes smoothly and completely to the corresponding primary amino-alcohols.

(3) When the aromatic portion is substituted by a phenolic hydroxyl or its methyl ether, reduction in acid stops at the amino-ketone stage. Further reduction to the amino alcohol may be accomplished in aqueous solution with a fresh catalyst, after isolation of the intermediate amino-ketone as its hydrochloride salt.

(4) The oximino group apparently is a readier receptor for hydrogen chloride, as is shown not only in the case of the phenolic derivatives, but also in some cases of α-oximinopropiophenone when 2/3 of the calculated hydrogen was taken up and the product proved to be the salt of the amino-ketone, $C_6H_5.CO.CHNH_2.CH_3$ (HCl).

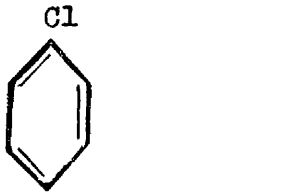
(5) The effect of hydrogen chloride is threefold:

a. Responsible for the hydrogenation of the oximino-group

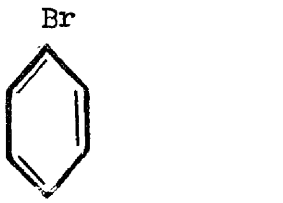
b. Marked effect on the rate of hydrogenation

c. Prevents formation of contaminating secondary and tertiary bases.

When the oximino-ketones contain a halogen substituted in the aromatic nucleus, an additional factor must be considered in their reduction, namely, the stability of the halogen to hydrogenation. Edkins and Linnell (65) studied the reduction of p-chloro and p-bromo-α-aminopropiophenone in an attempt to obtain compounds I and II.



(I)

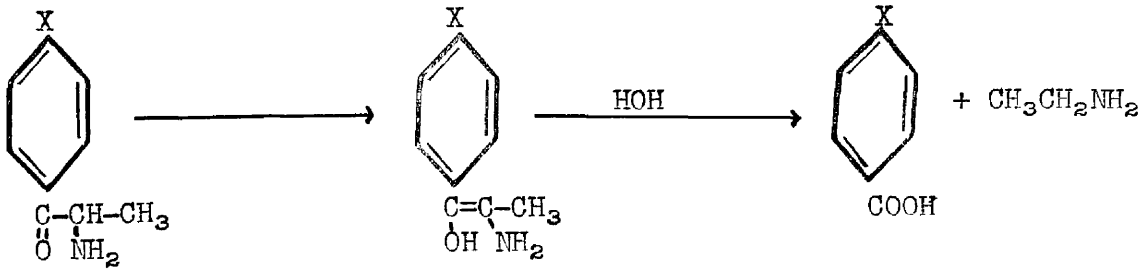


(II)

Aluminum amalgam in acetic acid, sodium in acetic acid, and magnesium in methyl alcohol, all yielded products which resisted attempts at recrystallization and which were nitrogen-free. Electrolytic reduction at different current densities produced no effect and the ketone was recovered unchanged.

Attention was then directed to catalytic hydrogenation, but the results were again unfavorable. Hydrogenation in the cold in acid aqueous medium, with palladinized-charcoal as the catalyst, yielded phenylpropanolamine from both the p-chloro-and p-bromo-α-aminopropiophenones. Attempts to avoid this loss of halogen by varying the conditions of the experiment were unsuccessful.

Attempts were then made to prevent the loss of halogen by performing the experiments in acid alcoholic solution. Under these conditions the absorption of hydrogen was very slow and the products obtained in almost theoretical yields were the corresponding halogenobenzoic acids. It appeared therefore that the reaction consisted of hydrolysis involving the break of the chain at the carbonyl group, thus:



In support of this contention they found that the reaction occurred equally well, though more slowly, in 97% alcohol or in water in the presence of the

catalyst, but in the absence of hydrogen. However, on shaking the amino-propiophenone with alcohol or water, without catalyst or hydrogen, only a trace of acid was obtained. The presence of catalyst therefore appeared to be essential.

The results of Hartung, Munch and Crossley (20) in the catalytic hydrogenation of p-chloro-α-oximinopropiophenone with a Pd-charcoal catalyst are not entirely in accord with those of Edkins and Linnell. In absolute alcoholic solution (containing three equiv. of HCl), the first 2/3 of the requisite hydrogen was taken up quite readily and then the rate dropped markedly, and at this time a heavy crystalline precipitate had formed which was presumed to be the amino-ketone hydrochloride. To facilitate solution of the product water (which as a rule was employed without deleterious effect in reducing the amino-ketone to the amino-alcohol) was added, and the catalyst fortified by the addition of more $PdCl_2$. The rate of hydrogen absorption increased rapidly and proceeded until four equivalents had been taken up. The product proved to be propadrine hydrochloride ($C_6H_5.CHOH.CHNH_2.CH_3$-HCl). In order not to reduce off the aromatic chlorine, it was found necessary to use large volumes of alcohol and to avoid the use of water.

Therefore in the catalytic hydrogenation experiments conducted in this investigation, it was necessary to employ conditions which would reduce the oximino and ketone groups but which would not result in the removal of the halogen from the benzene ring. These conditions are described under the individual compounds.

The following two catalysts were employed in the reductions.

Catalyst No.I was used in the initial reductions of the p-fluoro-oximino-ketone and was prepared as described under m-aminopropiophenone. In later experiments it was replaced by catalyst II which was more active.

Catalyst No. II. Levin (126) and Hartung and Reeve (131) have pointed out that the use of sodium acetate in the preparation of the palladium-charcoal produces a catalyst of "high activity." Therefore sodium acetate was employed in the preparation of this catalyst according to the following procedure.

Palladium chloride crystals (0.6 g.) were dissolved with the aid of heat in 10 cc. of water and 3 cc. of conc. hydrochloric acid. This solution was added to 3 g. of Norite (E.K. and Co.) to form a paste to which was added 90 cc. of water containing 12 g. of sodium acetate. This mixture was shaken in an atmosphere of hydrogen until saturated. The palladinized-charcoal was collected on a filter with suction, and washed thoroughly with distilled water and finally with absolute alcohol. The catalyst was kept under absolute alcohol, and was added to the reaction mixture as the alcoholic suspension (known concentration).

Reduction Mixture. This mixture was prepared by dissolving the oximino-ketone in absolute alcohol (commercial). Sufficient alcoholic hydrogen chloride to make the solution two normal in hydrogen chloride was added from a stock solution together with the alcoholic suspension of the catalyst. The mixture was then hydrogenated at approximately atmospheric pressure in an apparatus similar to that described by Hartung (108).

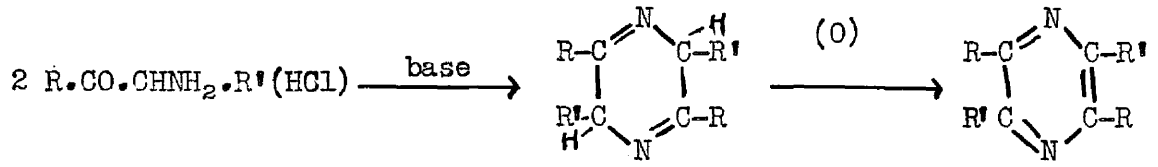
The stock solution of alcoholic hydrogen chloride was prepared by passing dry hydrogen chloride gas into absolute alcohol (commercial), the alcohol being weighed before and after the passage of the gas to determine the concentration of the solution. It was stored in a glass stoppered bottle in the refrigerator.

Two tests were employed to determine the presence of any intermediate reduction product (amino-ketone) in the compound isolated from the hydrogenation.

1. Reduction of Fehling's solution.. The pure amino-alcohols do not

reduce Fehling's solution, but form with it a crystalline precipitate (60). On the other hand, the incompletely hydrogenated product (amino-ketone) reduces Fehling's solution (30,60,65) with the formation of red copper oxide, and this fact as well as the measure of the hydrogen absorbed can be used in determining the completeness of the reduction.

2. Pyrazine Formation. Amino-ketones of the type, $R.CO.CHNH_2.R'$, are unstable when liberated from their salts, undergoing spontaneous condensation to dihydropyrazines which are readily oxidized to the more stable pyrazine derivatives (20,60,132,133).



dihydropyrazine pyrazine

The characteristic color changes accompanying these reactions may be used as an indication of the presence of amino-ketone. When a solution of its hydrochloride is made basic (NaOH or NH_4OH), the solution becomes cloudy, turns yellow, and the dihydropyrazine gradually precipitates as a bright yellow compound. On the addition of hydrochloric acid, the mixture assumes a fiery red color. The dihydropyrazine is converted to the more stable pyrazine on standing in the air, or more rapidly by the addition of mild oxidizing agents. The amino-alcohols, $R-CHOH.CHNH_2.R'$, however are stable as the free bases and do not give the above reactions.

Reduction of p-fluoro-α-oximinopropiophenone

In the initial experiments in which 5 g. (0.028 moles) of the oximino-ketone in 100 cc. of 2N absolute alcoholic hydrogen chloride was hydrogenated

with 3 g. of catalyst I, reduction ceased after only 1280 cc. of hydrogen (approx. 2 equiv. or 2/3 of the theoretical had been absorbed — 4 1/2 hours. At this point at which a crystalline precipitate (presumably the amino-ketone hydrochloride) was present in the reduction mixture, 50 cc. of distilled water was added to dissolve the precipitate, the catalyst was fortified by the addition of 0.15 g. of palladium chloride, and hydrogenation continued. The final third equivalent of hydrogen was absorbed in 3 hours. The catalyst was filtered off, the filtrate placed over conc. sulphuric acid in a vacuum desiccator attached to a water pump, and the solvent removed. The crude crystalline residue was dissolved in hot alcohol, the alcoholic solution cooled, and ether added. The fine colorless crystals of p-fluoropropadrine hydrochloride, $p\text{-}FC_6H_4.CHOH.CHNH_2.CH_3(HCl)$, melted at 222-3°, gave no tests for amino-ketone, and on permanganate oxidation produced p-fluorobenzoic acid. Yield 4 g. Nitrogen found — 6.61,6.73%; calculated for $C_9H_{13}NOFCl$ - 6.82%.

In one run the product was isolated, after the reduction had ceased at the 2/3 stage, and proved to be the amino-ketone hydrochloride, giving a dark red melt at 228-30° (dec.). Also, the use of water in the last phase of the hydrogenation did not cause the removal of the fluorine from the benzene ring.

In the subsequent reductions of this and the other compounds, using catalyst II, the relative rate of absorption of the first two equivalents of hydrogen was greater than in the above experiment. However, difficulty was experienced in completing the absorption of the third equivalent, in some cases heating of the reduction mixture with steam being necessary. The procedure follows.

To a solution of 9 g. (0.05 moles) of the oximino-ketone in 200 cc. of 2N absolute alcoholic hydrogen chloride was added 2 g. of catalyst II,

and the mixture hydrogenated. After 100 minutes, 2350 cc. of hydrogen had been absorbed (approx. 2 equiv. or 2/3 of theoretical) and the uptake of hydrogen ceased. At this point 100 cc. of distilled water was added to dissolve the precipitate which had formed, together with 2 g. of fresh catalyst, and hydrogen uptake was resumed. It was necessary to heat the flask with a steam bath from time to time to complete the reduction, approximately sixteen hours being required for the absorption of the third equivalent of hydrogen.

The catalyst was filtered off and the solvent removed by distillation under reduced pressure using a water bath maintained at about 25-35°. The yellowish crystalline residue was dried over conc. sulfuric acid in a vac. desiccator, and washed thoroughly with ether to remove the color and any unreduced compound. The crude p-fluoropropadrine hydrochloride was purified as follows:

A. Recrystallized from 70 cc. of absolute alcohol, m.p. 225-6°

B. A few grams of crystals A recrystallized from absolute alcohol, m.p. 225-6°

C. Ether added to filtrate A - m.p. 221-2°

D. Crystals C recrystallized from filtrate B + absolute alcohol, m.p. 225-6°

Total yield of p-fluoropropadrine hydrochloride - 8 g. (77.8%). Oxidation by permanganate gave p-fluorobenzoic acid, m.p. 183-3.5° after recryst. from hot water. Tests for amino-ketone were negative. Chlorine (as HCl). found—17.34, 17.19%; calculated for $C_9H_{13}NOFCl$ -- 17.27%.

Reduction of m-fluoro-α-oximinopropiophenone

A solution of 9 g. (0.05 moles) of the oximino-ketone in 200 cc. of 2N absolute alcoholic hydrogen chloride was hydrogenated, with 2 g. of catalyst II. After 95 minutes, 2310 cc. of hydrogen (approx. two equiv. or

2/3 of the theoretical) had been absorbed and the uptake of hydrogen ceased. One gram of fresh catalyst and 50 cc. of distilled water was added to the reduction mixture, and hydrogenation continued. An additional 1110 cc. of hydrogen was absorbed in about six hours.

The product was isolated as described for the para-compound, and the yellowish crude crystals washed thoroughly with ether, which removed most of the color. Purification was carried out as follows:

A. The crude crystals were dissolved in 70 cc. of hot absolute alcohol, the solution filtered and cooled in the refrigerator. The colorless crystals obtained melted at 210-10.5°.

B. A few grams of crystals A were recrystallized from absolute alcohol, m.p. 210.5-11°.

C. Ether was added to filtrate A, colorless crystals were obtained, m.p. 205-6°.

D. Product C was recrystallized from mother liquor B, m.p. 211-11.5°.

E. All of the mother liquors were combined, evaporated to dryness on a steam bath, and 10% sodium hydroxide added to the yellow residue. The liberated free amine was extracted with benzene, and the benzene solution washed with water and dried over anhydrous sodium sulphate. In passing dry hydrogen chloride into the solution, the hydrochloride salt, m.p. 209-9.5° was obtained.

Total yield of m-fluoropropadrine hydrochloride, m-FC_6H_4.CHOH.$CHNH_2$.CH_3(HCl), was 7 g. (68%). The purified compound gave no tests for amino-ketone. Chlorine (as HCl) found - 17.42,17.34%; calculated for $C_9H_{13}NOFCl$-17.27%.

Permanganate oxidation gave m-fluorobenzoic acid, m.p. 124-5°. A mixed melting point of this acid with pure benzoic acid was 112-13°.

Reduction of o-fluoro-α-oximinopropiophenone

A solution of 5.4 g. (0.03 moles) of the oximino-ketone in 150 cc. of 2 N absolute alcoholic hydrogen chloride was hydrogenated, using 2 g. of catalyst II. After 105 minutes, 1300 cc. of hydrogen had been absorbed (approx 2/3 of theoretical) and the uptake of hydrogen ceased. At this point 50 cc. of distilled water and 1 g. of fresh catalyst was added to the reduction mixture and the hydrogenation continued. An additional 750 cc. was absorbed in about 4 hours.

The product was isolated as described for the p-fluoro-compound and thoroughly washed with ether. The almost colorless crystals were purified as follows:

A. The crude product was dissolved in 50 cc. of absolute alcohol, the solution filtered, and cooled in the refrigerator. The fine colorless crystals obtained melted at 231.5-2.5°.

B. A few grams of product A was recrystallized from absolute alcohol, m.p. 232-2.5°.

C. Ether was added to filtrate A; crystals obtained, m.p. 228-9°.

D. Crystals C were recrystallized from the mother liquor of B, m.p. 231-31.5°.

The total yield of o-fluoropropadrine hydrochloride, $o\text{-}FC_6H_4.CHOH.CHNH_2.CH_3(HCl$ was 4 g. (65%). The purified compound gave no tests for amino-ketone. Chlorine (as HCl) found - 17.32, 17.46%; calculated for $C_9H_{13}NOFCl$ - 17.27%.

Permanganate oxidation gave o-fluorobenzoic acid, m.p. 122-3° from heptane. A mixed melting point of this acid with pure benzoic acid was 107-8°.

Reduction of p-chloro-α-oximinopropiophenone

In the light of the experience of previous investigators, the use of water in the final stage of the reduction of the chlorine substituted com-

pounds was avoided.

A solution of 16.8 g. (0.085 moles) of the oximino-ketone in 500 cc. of 2 N absolute alcoholic hydrogen chloride was hydrogenated, using 3 g. of catalyst II. The hydrogen absorption ceased after about 3 hours at which time 3745 cc. of hydrogen (approx. 2/3 of the theoretical) had been taken up, and a heavy crystalline precipitate was present in the reduction mixture. The catalyst was fortified by the addition of 0.3 g. of palladium chloride, the reduction mixture heated with steam to about 75, and shaking started. The absorption of the third equivalent of hydrogen was slow and required about 17 1/2 hours, during which time it was necessary to heat the flask with steam from time to time.

The reduction product was isolated as described for the p-fluoro-compound and the crude yellow crystals were washed thoroughly with ether.

A. Recrystallization from absolute alcohol gave colorless crystals, m.p. 239-40°.

B. Product A was recrystallized from absolute alcohol, m.p. - 244-5°; reported m.p. - 245° (20).

C. Ether was added to the combined mother liquors of A and B. The colorless crystals obtained melted at 233-4°.

D. Product C was recrystallized from absolute alcohol, m.p. - 243-4°.

The total yield of p-chloropropadrine hydrochloride, $p\text{-}ClC_6H_4.CHOH.CH_3(HCl)$, was 13 g. (69%). The purified product gave no tests for amino-ketone. Chlorine (as HCl) found - 16.23, 16.11%; calculated for $C_9H_{12}NOCl_2$ - 15.99%.

Permanganate oxidation produced p-chlorobenzoic acid.

Reduction of m-chloro-α-oximinopropiophenone

A solution of 10 g. (.05 moles) of the oximino-ketone in 500 cc. of 2 N absolute alcoholic hydrogen chloride was hydrogenated, using 2 g. of catalyst II. After 2 hours, 2330 cc. of hydrogen (approx. 2/3 of the theo-

retical) had been absorbed and the absorption of hydrogen became very slow. One gram of fresh catalyst was added and the flask was heated with steam from time to time until the third equivalent had been taken up; this required an additional eight hours.

The product was isolated as before and the crude crystals obtained were washed with ether.

A. The crude crystals were dissolved in 40 cc. of hot absolute alcohol, filtered, ether added until the solution became cloudy, and the mixture cooled in the refrigerator. The colorless crystals obtained melted at 180-181°.

B. Product A recrystallized from absolute alcohol, m.p. 183-184°.

C. More ether was added to filtrate A, the colorless crystals obtained melted at 160-2°. Recrystallized from amyl alcohol, m.p. 181-2°.

Total yield of m-chloropropadrine, m-ClC_6H_4.CHOH.$CHNH_2$.CH_3(HCl), was 7 g. (63%). The purified product gave no tests for amino-ketone. Chlorine (as HCl) found - 16.13, 16.21%; calculated for $C_9H_{13}NOCl_2$-15.99%.

Permanganate oxidation gave m-chlorobenzoic acid, m.p. 154-4.5°.

Reduction of o-chloro-α-oximinopropiophenone

A solution of 10 g. (0.05 moles) of the oximino-ketone in 400 cc. of 2 N absolute alcoholic hydrogen chloride was hydrogenated, using 2 g. of catalyst II. After about 2 1/2 hours, 2420 cc. of hydrogen (approx. 2/3 of the theoretical) was absorbed and the uptake of hydrogen was very slow. An additional 1 g. of fresh catalyst was added and reduction continued, heating with steam from time to time being required. The third equivalent of hydrogen was absorbed in about 17 1/2 hours.

After isolation as previously described and washing with ether the crystalline product weighing 9 g. was purified as follows:

A. Recrystallized from absolute alcohol, m.p. 176-7° (dark brown melt).

B. Ether added to filtrate A, colorless crystals, m.p. 177-8° (dark melt).

C. Products A and B combined and recrystallized from a equal mixture of ethanol and amyl alcohol, m.p. 182-3° (dark brown melt).

D. Ether added to mother liquor of C, crystals obtained melted at 182-3°.

The following facts concerning the above product were determined.

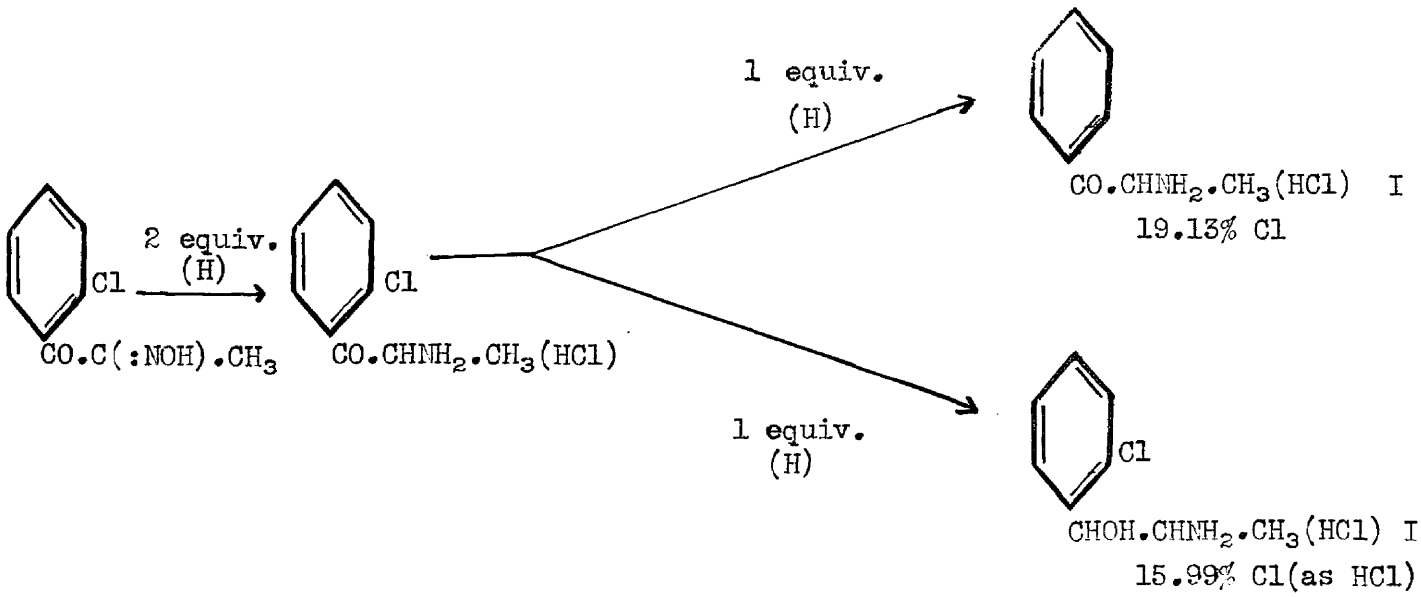
1. When an aqueous solution of the hydrochloride was made basic with ammonium hydroxide the yellow color change characteristic of the dihydropyrazine was produced. However, the addition of hydrochloric acid to the yellow mixture did not produce the fiery red color characteristic of the pyrazine reaction. For this reason the pyrazine reaction was not definite.

2. The compound reduced Fehling's solution.

3. Permanganate oxidation gave a small amount of o-chlorobenzoic acid.

4. Analysis for chlorine (as HCl) showed 17.20%.

The hypothetical compounds which might be obtained by the absorption of 3 equivalents of hydrogen is indicated below:

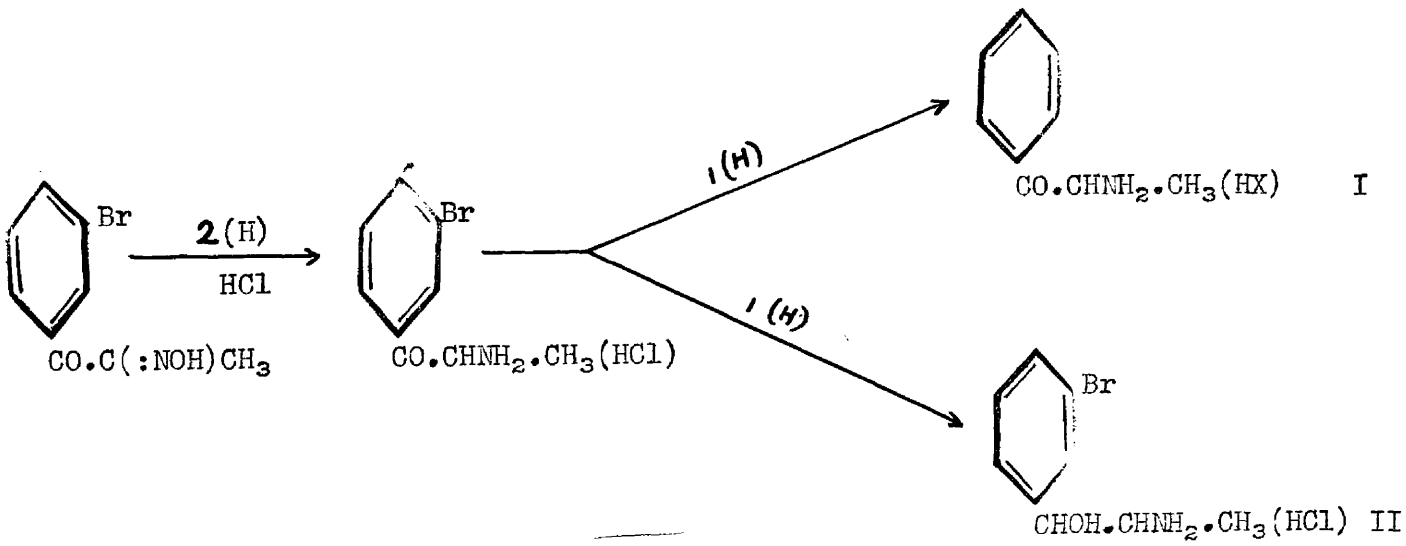


Although the evidence is insufficient to support a definite conclusion as to the structure of the reduction product, the assumption that it is a mixture of compounds I and II seems to agree with the data obtained.

Reduction of m-bromo-α-oximinopropiophenone

Using 2 g. of catalyst II, 12 g. (0.05 moles) of the oximino-ketone was hydrogenated in 400 cc. of 2 N absolute alcoholic hydrogen chloride. The first two equivalents of hydrogen were absorbed in about three hours. To the mixture was then added 1 g. of fresh catalyst and hydrogenation continued, it being necessary to keep the mixture heated with a steam bath. The third equivalent of hydrogen was absorbed in about six hours and the product was isolated and washed with ether. The crude crystalline product was recrystallized from 50 cc. of an equal mixture of sec.-butyl and amyl alcohol and melted at 162-3°. A second recrystallization from sec.-butyl alcohol gave colorless crystals, m.p. 164-5°.

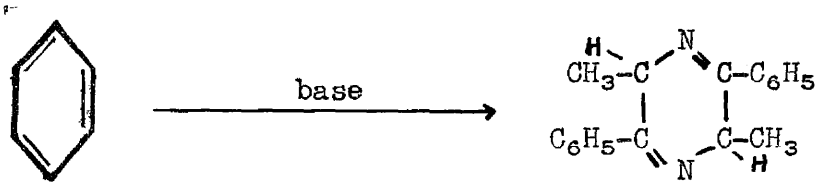
From the results of experiments conducted on the product, it was found that this product was not the desired m-bromo-propadrine hydrochloride. On considering the following courses which the absorption of three equivalents of hydrogen might follow,



it was concluded that the reduction had proceeded according to (I). This conclusion was substantiated by the following evidence:

1. The production of benzoic acid, rather than m-bromobenzoic acid, by permanganate oxidation of the product showed that the bromine had been removed from the aromatic ring. The identity of the benzoic acid obtained was verified by a mixed melting point with a sample of known benzoic acid.

2. Tests for amino-ketone were positive. The yellow dihydropyrazine, obtained by treating the reduction product with concentrated ammonia, melted at 94-6 after recrystallization from dilute alcohol. Gabriel (132) reported a melting point of 99 -100° for the dihydropyrazine which he obtained by the reaction:



$CO.CHNH_2.CH_3(HCl)$

3. Quantitative analyses for halogen (as HX) indicated that the product of the reduction was a mixture of the hydrochloride and hydrobromide salts. The presence of bromine (as HBr) was verified by checking the silver halide, obtained in the Volhard analysis, qualitatively for bromide ion.

Therefore under the conditions of the hydrogenation used in this investigation, it was not found possible to prevent the loss of bromine from the aromatic ring, and the desired m-bromo-compound was not obtained.

In view of this result, and that experienced with the o-chloro-compound, the reduction of the o- and p-bromo-oximino-ketones was not carried out. This problem is reserved for future investigation when it is hoped that the proper reduction conditions may be established.

SUMMARY

(1) A literature survey correlating the relationship between molecular structure and physiological activity of the sympathomimetic amines is presented. The structures producing optimum physiological activity of these compounds is discussed.

(2) A literature survey of the pharmacology of propadrine is given together with a comparison of the physiological activities of its ring substituted derivatives.

(3) A literature survey of the physiological effects produced by the introduction of halogens into the aromatic nucleus of pressor amines is also given.

(4) With the object of synthesizing a series of halogen ring substituted propadrines:

A. The following ketones were first prepared.

1. o-
2. m-
3. p-

— fluoropropiophenone

4. o-
5. m-
6. p-

— chloropropiophenone

7. o-
8. m-
9. p-

— bromopropiophenone

B. These ketones were converted into the following corresponding α-oximino ketones by a general nitrosation procedure.

10. o-
11. m-
12. p- — fluoro-α-oximinopropiophenone

13. o-
14. m-
15. p- — chloro-α-oximinopropiophenone

16. o-
17. m-
18. p- — bromo-α-oximinopropiophenone

Of these products (1 to 18) all except 1,6,7,8,9,15, and 18 have not previously been reported.

C. Catalytic hydrogenation of compounds 10, 11, 12, 14, and 15 resulted in the production of the desired halogen amino-alcohols (halogen propadrines), whereas in the case of compounds 13 and 17 reduction did not produce the desired products and resulted in loss of the halogen from the ring.

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