THE SYNTHESIS OF ANALOGS OF MESCALINE

By

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INTRODUCTORY

The study of the synthesis and uses of therapeutic agents is a matter of vital importance. Disease means suffering and pain; and chiefly for this reason diseases should be combated. With the progress of civilization, man as an animal is growing less resistant to infections (1) and has come and in the future will come more to depend upon synthetic medicinals.

The question of how to obtain the most suitable chemical compound for the production of desirable or the removal of undesirable conditions naturally arises from any consideration of the physiological activity of chemical substances. It is obviously impractical to try all possible compounds; so that the only alternative which remains is to attempt a correlation of the known activities of substances with some other property or properties in such a manner that the physiological activities of new and hitherto unprepared compounds can be anticipated within reasonable limits.

It is not unreasonable to adopt the thesis that biological response is connected in some fashion with the chemical nature of the substances. Leake (2) has proposed to call this relation between chemical structure and pharmacological action, biochemorphology. While a consideration of biochemorphology is fundamental, it may not necessarily be logically satisfactory for with the development of organic chemistry and pharmacology, it became apparent that many compounds not at all related chemically were capable of eliciting the same pharmaco-

logical response (3).

Blake (4) courageously began in 1841 to inquire into the possible relationship between chemical constitution and biological action, using inorganic salts whose physico-chemical properties were comparatively well known at that time. He had already found that drugs act in the mammalian body only after reaching the responsive tissue and not indirectly by reflex nervous mechanism (5). His extension of this problem led to a consideration of the important matter of the absorption and distribution of drugs and of the rates at which these processes may proceed. Blake's work, gross though it was, led him to conclude that the characteristic pharmacological effect of an inorganic salt is due more to the electropositive rather than to the electronegative ion, that there is a relation between the properties of elements and the biological action of their compounds, and that with the increase of atomic weight in isomorphous groups of elements there is an increase in intensity of action of corresponding salt.

Blake's fundamental approach to the relation between chemical constitution and pharmacological action was extended to organic compounds by Crum Brown and Fraser (6). They demonstrated in 1868 that by a slight and constant chemical change, tertiary bases of widely differing physiological activities could be converted into quaternary bases of almost uniform physiological activity (curare-like) which in many cases differed from that of the parent tertiary base. This discovery formed the commencement of a long series of attempts to

correlate chemical structure with physiological activity. At the outset it appeared that some sort of systematization was at hand and that by skillful prediction, the properties of a new therapeutic substance could be ascertained from inspection of its chemical formula.

Richardson (7) reported data showing that with increase in the length of a carbon chain of the alkyl series, physiological activity uniformly varied. Loewi and Meyer (8), as well as Dakin (9) examined many of the ketones of the general formula: $(OH)_2C_6H_3COCH_2NRR'$ and the corresponding secondary alcohols as part of the program in their study of the synthesis of epinephrine. They found that in most reduction to the secondary alcohol greatly increased the epinephrine-like action, but where R and R' represent complex radicals, Dakin found no such increase of activity on reduction. Although no great generalizations have appeared, the scope of the effort was indicated by such survey as has been made by Oswald (10) and Frankel (11).

Some years after the discovery of the pressor effect of epinephrine, Abelous, Ribaut, Soulie and Toujans (12) reported that a similar effect is produced by an extract of putrid meat. Their brief note on this observation excited the curiosity of Barger and Dale; and after allowing a few pounds of steak to putrify, they were able to confirm the findings of the French authors. A large and transitory rise of blood pressure was rapidly produced in the decerebrate cat by intravenous injection of an extract of the putrid meat. They at once began an attempt to isolate the active principle responsible

for this physiological action. Results of the investigation culminated in their masterly presentation (13) which today is regarded as the starting point in the study of amines possessing properties which mimic the actions of stimulants for sympathetic nervous system.

In the correlation of chemical structure and biological activity of the compounds of the sympathomimetic type, much work has since been done notably by Trendelenburg, Chen et al, Hartung et al, Alles, Tainter, Suter and numerous others.

As part of the general problem of biochemorphology, the relation of the physical properties of substances to their biological effects has also been considered especially under the stimulus of Loeb (14). Arrhenius (15) made attempts to correlate the action of drugs purely through the application of the principles of physical chemistry. As time went on, research uncovered the complex nature of this problem of correlation. It became apparent that a single path of approach could not adequately give satisfactory explanations for all the reactions taking place in the responsive tissues. Perhaps it may be profitable to correlate the pharmacological response in a detached attitude of scientific aloofness unbiasedly combining multitudinous array of data presented from the domain of physical (15), enzymic (16,17,18,19), stereochemical (20,21), and atomic structural (22,23,24) considerations, as well as the consideration of gross chemical structures (10,11,13).

SURVEY OF BIOLOGICAL LITERATURE

Studies on compounds that produce a rise in blood pressure appear to indicate that certain definite structural arrangements of the molecule are essential. For example, it has been established that:

1- The optimum skeleton for pressor activity is found in compounds having a phenyl group and an amino or a substituted amino group attached to adjacent carbons of an aliphatic chain (13,25);

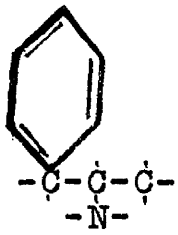
2- Compounds containing two or three carbons in the aliphatic chain possess maximum pressor activity (26,27);

3- Compounds with an amino group or a substituted amino group on the secondary carbon atom of the side chain are active on the blood pressure after oral administration (16,28);

4- A secondary alcoholic hydroxyl attached to the carbon bearing the phenyl serves to detoxify and to increase the pressor activity of the molecule (13, 25, 26);

5- Primary amines tend to be more active and less toxic than the corresponding alkylated secondary amines. If the size of the alkyl group on the amine is increased, there is a corresponding decrease in the activity and increase in the toxicity (26,29).

These conclusions enable the following graphical skeleton to be drawn:



It becomes apparent that variation of magnitude on the skeletal structure is restricted and that any further change must be made on the aromatic ring. Investigations showing the effect of variation on the phenyl nucleus have been carried on since the time of Barger and Dale who began with phenolic hydroxyl variation. These nuclear variations will be surveyed in the following order:

a- Effect of nuclear hydroxyl group

b- Effect of nuclear alkyl group

c- Effect of nuclear halogen group

d- Effect of nuclear amino group

e- Effect of nuclear methoxyl group

<u>a- Effect of Nuclear Hydroxyl Group</u>:

Hartung (30) has excellently reviewed the effect of hydroxyl substitution in the nucleus. The relation of structure to activity has been most extensively worked out for the monohydroxyl nuclear substitutions.

Barger and Dale (13) were the first to investigate the role of phenolic hydroxyl group. They compared the three monohydroxy derivatives of β-phenethylamine and concluded that the ortho was no more active than β-phenethylamine itself,

that meta- and para-hydroxyl groups are of equal influence in enhancing activity, that maximum activity results when both are present, and that the introduction of the third, or ortho phenolic hydroxyl decreases activity.

Chen, Wu and Henriksen (26) from their experience with epinephrine and the conclusions of Barger and Dale, suggested that the presence of hydroxyl groups in the phenyl nucleus confers "intensity of action" and predicted that p-hydroxyphenyl-1-amino-2-propanol might combine the desirable properties of intensity of action, minimum toxicity and greater activity of the primary amine and duration of action and oral activity conferred by the three carbon atom side chain. The synthesis of such a compound was accomplished by Hartung (31) in 1930 and the pharmacological predictions verified.

In the monohydroxyephedrine series, it has been shown that the characteristic responses after ergotaminization and cocainization indicate that the ortho-phenolic compound is most like ephedrine itself; that the meta-isomer is least like ephedrine and that it has begun to take on the properties of epinephrine; and that the para-derivative is somewhere intermediate between the two (33).

The introduction of phenolic hydroxyl groups into phenylpropanolamine tends to reduce the duration of pressor response. The ortho-hydroxyl increases toxicity almost twofold and probably decreases the potency, the meta-hydroxyl increases the activity about threefold and the toxicity about four times, the para-phenolic hydroxyl increases the activity and decreases the toxicity (30,31).

In the phenylisopropylamine series, Woodruff and Conger (34) prepared the three monohydroxy structural modifications for the purpose of pharmacological study. Literature search, since their publication, reveals no pharmacological data.

Generally, in modifying the pressor activity, ortho-hydroxyl groups are least active, as originally reported by Barger and Dale. However, contrary to their conclusions, meta- and para-hydroxyl groups are not identical in effect. Ehrhart (35) and Schaumann (30,36) have found that m-hydroxyephedrine is a stronger pressor than the para-isomer. Hartung, Munch, Miller and Crossley (31) observed that m-hydroxyphenylpropanolamine is at least twice as strong as p-hydroxyphenylpropanolamine. Kuschinsky (37) reported that m-sympatol (neo-synephrine) is five times as active as the para derivative (synephrine). Hence it appears from these observations that most of the intensifying effect is contributed by the meta-hydroxyl group.

The simultaneous introduction of two hydroxyl groups in the aromatic ring gives a series of qualitatively interesting type of compounds. 2,4-Dihydroxyphenylethanolamine was found by Boruttau (38) in 1912 to have but slight effect on blood pressure even in very large doses. Equally inactive is 2,4-dihydroxyphenylpropanolamine (31) which at larger doses gave a depression of the blood pressure. Perhaps, survey of these data together with the original findings of Barger and Dale, namely that ortho-derivatives are least effective, has warned the organic medicinal chemists to stay clear of any resorcinol

derivatives contemplated as pressor agents.

Only few references are made to 2,5-dihydroxy derivatives. Boruttau (38) prepared 2,5-dihydroxyphenylethanolamine at the time when he prepared the 3,4-dihydroxy derivative. He found that the quinol derivative was more active than the resorcinol derivative but not as active as tyramine or p-hydroxyphenylethanolamine. Apparently the 2,5-positions simultaneously are not too favorable structural modifications for optimum physiological desirability. In the N-methylated β-phenethylamine series, Hjort (39) found that of the dihydroxy substituted compounds, the 2,5-isomer is the most toxic, about the same in toxicity as the parent amine, the 3,4-isomer is the least toxic and the 2,3-compound occupies an intermediate position, and that 2,3-isomer is a very good pressor agent.

Barger (40) and Tainter (41) describe 3,4-dihydroxyphenylethylamine to be about 1/75 to 1/66 as active as epinephrine. 3,4-Dihydroxyphenylethanolamine was described as demonstrating virtually all the characteristic reactions of epinephrine; Schultz (42) and Barger and Dale (13) found it to be about a little less than one and one-half times as active as epinephrine. About twenty years later, Tiffeneau (43) checked the pharmacological activity of the same compound and described it to be twice as active as epinephrine. In the phenylpropanolamine series, Hartung and his associates (31) found that the racemic compound, 3,4-dihydroxy derivative, had toxicity in rabbit 1/100 as great as that of epinephrine and that its pharmacological behaviour was qualitatively indistinguishable from that

of epinephrine; however, it possessed a weaker action being about 1/12 as active as (-)-epinephrine. Schaumann (36) reports the activity of this derivative to be about 1/6 to 1/3 as active as (-)-epinephrine. Foster (44) in his tabular summary, ascribes its activity to be 1/4 the activity of epinephrine. 3,4-Dihydroxy derivative of the ephedrine series was investigated by Schaumann (33) and found to give many of the characteristic epinephrine-like reactions.

During the transition from one hydroxy structural modification to another, it became pharmacologically noticeable that structural juggling also modified the mechanism through which the physiological action is produced. By a carefully developed complementary procedure of cocainization and ergotaminization, Tainter investigated a series of sympathomimetic compounds and subdivided them into three classes (45):

> 1- Those compounds which act like epinephrine by stimulating sympathetic innervations...sympathicotropic.
>
> 2- Those compounds which like barium and pitressin stimulate muscles directly...musculotropic.
>
> 3- Those compounds whose actions are intermediate between the two not completely satisfying the criteria which establish the sympathicotropic and musculotropic groups.

Whether or not the classification is absolute is a matter of time and test. In any event, observations seem to indicate that ephedrine, for example, is quite unlike epinephrine in its mode of action. It may not be too drastic in thought to listen attentively to Schaumann (33) who suggests that there is a gradual change from a distinctly ephedrine-like reaction to an epinephrine-like reaction as the substitution of a single hydroxyl group is shifted from ortho- to para- to meta-, the simultaneous introduction of both the meta- and para-hydroxyl groups conferring sympathicotropic reaction.

In view of the unique physiological response which the meta-positions are capable of stimulating, it is rather surprising that very little investigation has been made in the series of 3,5-dihydroxy derivatives. In fact, literature is conspicuously devoid of reports of this series of derivatives.

Introduction of the third hydroxyl group to the aromatic ring elicits no improvement in physiological responses. It is very true that of the four possible isomeric forms only the 2,3,4-trihydroxy derivative seems to have been studied. Therefore it is not possible to draw any generalization. However Barger and Dale (13) found in their work with β-phenethylamine that the introduction of the third or ortho hydroxyl group decreases the activity. 2,3,4-Trihydroxyphenylethanolamine, synthesized by Hinsberg (46) in 1923 and covered by German patent (47), was found to be inactive. Of the three remaining isomeric positions the 3,4,5-trihydroxy derivative may be anticipated to have interesting physiological properties.

b- Effect of Nuclear Alkyl Group

Since Barger and Dale showed that possesion of the skeleton of β-phenethylamine is the primary requirement for the manifestation of sympathicotropic properties, much work has been done to determine the effect of substituents attached either to the nucleus or to the side-chain of the parent molecule. In such study, alkyl groups have received their share of attention when attached to either carbon or nitrogen in the side-chain, but data are not so abundant in the study of the effect of alkyl groups attached directly to the nucleus.

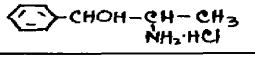
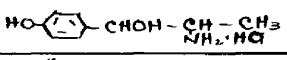
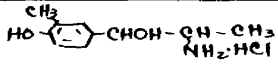
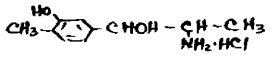
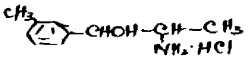
The p-methyl, p-ethyl and p-butyl derivatives of ephedrines have been prepared and were described by Ehrhart (35) in 1930 to be more toxic and having less circulatory effect than ephedrine. A year earlier, de Burnaga Sanchez (48) had observed that p-methylephedrine was about 20% more toxic and at the same time less active than ephedrine itself.

Similar influence of methyl groups was noted in the para-position of propadrine by Hartung and Munch (27,49). They learned that the pressor activity was reduced to about 3/5 and toxicity increased to about threefold that of ephedrine. They investigated further (52) and found that a methyl group introduced to the meta position of both propadrine and p-hydroxypropadrine makes the new compounds decidedly more toxic and the activity less effective. Tainter (53) reported that m-methylpropadrine as having only 35% of the pressor activity of the unsubstituted parent substance. These reports agree rather well with the findings of Barger (40) who observed that meta-methyl in tyra-

mine decreases activity. Hartung, Munch, Miller and Crossley (31) found that the introduction of a methyl group into phenolic derivatives of phenylpropanolamine produced an interesting pair of compounds possessing unexpected properties. The 3-methyl-4-hydroxyphenylpropanolamine was found to be twice as active and about four times as toxic as the parent compound; the 4-methyl-3-hydroxy isomer was also twice as active but somewhat less toxic than phenylpropanolamine. These results are surprising in view of the previously noted observations that meta- and para-methyl substitutions decrease pressor activity and increase toxicity. Other interesting anamolies can be noted from the following table taken from Hartung, Munch, Miller and Crossley (31):

TABLE I

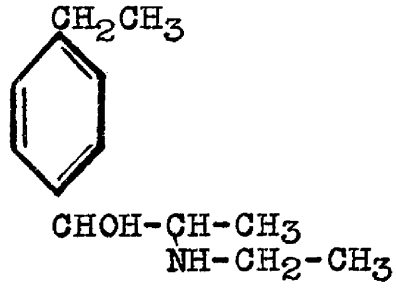
RELATIVE STUDY OF SUBSTITUTED PROPADRINES

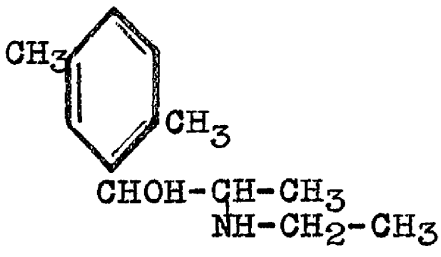
	MLD Intraven. Rabbit	Relative Pressor Activity
	75 mg./Kg.	1
	100-125	1.5
	20	2
	90	2
	16	3

Speer and Hill (54) extended the investigation to the alkylated series of β-phenethylamine and the N-methyl-β-phen-

ethylamine. They prepared p-methyl, p-ethyl, p-benzyl, p-phenethyl derivatives of the β-phenethylamine series; and p-methyl, m-methyl, o-methyl, p-ethyl, p-benzyl, o-benzyl, p-phenethyl derivatives of the N-methyl-β-phenethylamine series. These new compounds were pharmacologically evaluated by Hambourger and Jamieson (55). They found that in the primary amine series, a methyl group in the para-ethyl group caused a moderate decrease in the pressor effect; in the N-methylamine series, a methyl group in either the para- or meta-position reduced the activity slightly, an ortho-methyl group reduced it greatly, while para-ethyl substitution was associated with either a weak pressor action or a definite depressor activity, and those derivatives containing a second phenyl ring to be comparatively inactive with probable depressor tendency.

Several compounds with aryl and other alkyl substitutions have been prepared. Manske and Johnson (56) reported the synthesis of the following two compounds but physiological properties concerning them are lacking,





Macklis and Blanchard (57,58) synthesized 1-xenyl-2-aminopropanol and gave a preliminary report that its pressor activity was approximately 1/3 that of ephedrine. For the same com-

pound which Hartung, Munch and Crossley (52) had prepared few years prior, an activity of "trace" has been assigned expressed in terms of the parent compound, propadrine, and a toxicity four times as much.

α-Napthyl- and β-napthyl-2-aminopropanol derivatives were synthesized and investigated during the course of a study of ring substituted propadrines. The α-derivative was found to be more active than the β-isomer; however, both were more toxic and less active than propadrine itself.

Results thus far would seem to indicate that alkyl substitution in the aromatic nucleus reduces the activity and enhances the toxicity except in the cases of hydroxy substituted propadrines as noted by Hartung and co-workers (31).

c- Effect of Nuclear Halogen Group

An exhaustive literature survey of the effects produced by the introduction of halogens into the aromatic ring of the physiologically active pressor amines has been made by Zenitz (59). Prior to the time Zenitz began his work on the halogen ring-substituted propadrines, there had been very limited number of halogen derivatives prepared and were inadequately studied.

Barger (40) had prepared a series of para-substituted β-phenethylamine, among them being the p-chloro-β-phenethylamine. Pressor effect of para-chloro derivative was found to be more active than the non-substituted base, and having about one-third of the activity of tyramine. Tainter (60) in 1930 re-investigated the same series of Barger and found that p-chloro-β-phenethylamine was about half as active as tyramine. Since

tyramine (p-hydroxy-β-phenethylamine) is roughly five times as active as β-phenethylamine itself, this would indicate that the effect of the chlorine in the phenyl nucleus compares favorably with that of a phenolic hydroxyl group in the para-position. Buck (61) prepared the ortho-chloro derivative of β-phenethylamine in 1933 but no pharmacological data have appeared subsequent to this publication of the synthesis of the product.

The only studies of the effect on physiological properties of the introduction of fluorine into a pressor molecule were those reported by Hansen (62) and Suter and Weston (63). Hansen worked on the halogenated amino ketones and not on amino alcohols but the results that he uncovered agree well in principle with those of Suter and Weston. The latter investigators prepared and studied the effect of para-fluorine substitution in β-phenethylamine, α-methyl-β-phenethylamine and β-phenethylmethylamine and found that the fluorine substituted compounds were more toxic than the unsubstituted molecules in mice by oral administration. Animals used in the assay seem to display great deal of animal variation. They report the use of dogs, rabbits and guinea pigs, and found in general that the effect of the compounds was depressor in rabbits and pressor in dogs and guinea pigs. In dogs, p-fluoro-β-phenethylamine, α-methyl-p-fluoro-β-phenethylamine showed similar pressor activity while N-methyl-p-fluoro-β-phenethylamine was more active than either of the two. The activities of these compounds may be graphically summarized:

In dogs:

$CH_2-CH_2NHCH_3$

N-Methyl-p-fluoro- -phenethylamine

more active than

$CH_2-\underset{NH_2}{CH}-CH_3$

α-Methyl-p-fluoro-β-phenethylamine

$CH_2-\underset{NH_2}{CH_2}$

p-Fluoro-β-phenethylamine

In guinea pigs:

$CH_2-\underset{NH_2}{CH}-CH_3$

α-Methyl-p-fluoro-β-phenethylamine

more active than

$CH_2-\underset{NH_2}{CH_2}$

p-Fluoro-β-phenethylamine

$CH_2-\underset{NHCH_3}{CH_2}$

N-Methyl-p-fluoro-β-phenethylamine

$CH_2-\underset{NH_2}{CH}-CH_3$

α-Methyl-β-phenethylamine

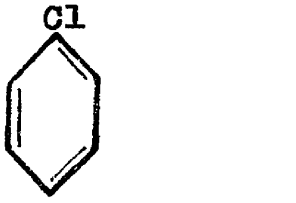
Schiemann and Winkelmuller (64) have described the synthesis of m-fluoro-β-phenethylamine. Kondo and Ishiwata (65) prepared the m-bromo-β-phenethylamine but pharmacological data for both of these compounds are lacking.

In the dihalogen substitution series, Glynn and Linnell (66) studied 3,4-dichloro-phenylethanolamine and found it to be 1/250 to 1/200 as active as epinephrine; and its toxicity to be about 1/240 that of (-)-epinephrine. From the data of Barger (40) phenylethanolamine is about 1/350 to 1/233 as ac-

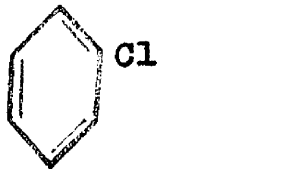
tive as dl-epinephrine. This would mean that 3,4-dichloro derivative of phenylethanolamine is approximately 1.2 to 1.4 times more active than the phenylethanolamine itself. Here again the effect of dihalogen substitution compares favorably with the effect produced by dihydroxy-substitutions on positions 3 and 4.

Among other compounds of this general type which have been prepared are 3,5-dichlorotyramine, 3,5-dibromotyramine and 3,5-diiodotyramine. No reference was found as to their pressor activity except for 3,5-diiodotyramine which was found to have an action similar to that of the thyroid by Abelin (67).

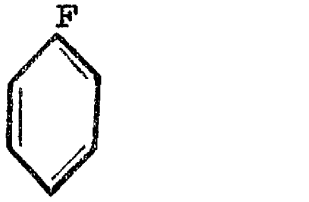
Zenitz (59) in 1940-1942 prepared a series of monohalogen ring substituted propadrines for future pharmacological study. His list included the following compounds:



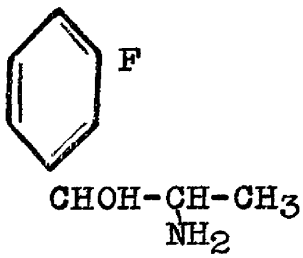
p-Chloropropadrine



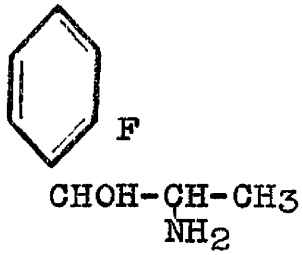
m-Chloropropadrine



p-Fluoropropadrine



m-Fluoropropadrine

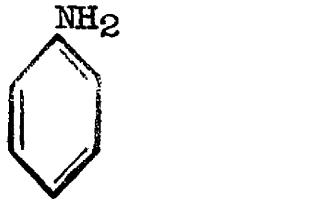


o-Fluoropropadrine

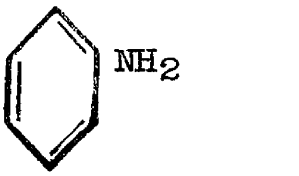
d- Effect of Nuclear Amino Group

The effect produced on the physiological properties by the introduction of amino group into the aromatic nucleus has been nicely reviewed by Foster (44). At the time Foster began his work on the improved method of synthesis of p-aminopropadrine and its derivatives, there were only few nuclear amino substituted derivatives available. They were:

p-Aminoephedrine



p-Aminopropadrine



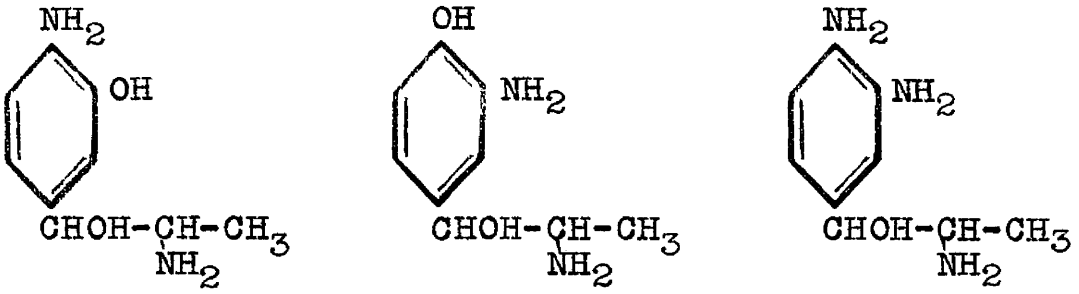
m-Aminopropadrine

Of the three only p-aminoephedrine ("Ephetonal") seems to have received any study. It is described to have a greater sympathetic action and one-third to one-half the toxicity of ephedrine by Mayer (68). Para-aminopropadrine is reported to possess ephedrine-like action and therapeutic properties of m-aminopropadrine are said to compare favorably with those of "Ephetonal" by Oberlin (69) and Dalmer and Oberlin (70).

Foster, in his thesis, raises an interesting question:

> These amino compounds, however, deserve more attention than they seem to have received thus far. For instance, the amino group, according to Franklin, is the ammono-analog of the hydroxyl group, and like the hydroxyl group when introduced into an organic molecule, confers lyophilic properties. It should prove enlightening to learn whether these structurally 'isosteric' substituents produce identical or similar modifications in the physiological reactivity. It should prove interesting and not unexpected to find considerable parallelism between the properties and activities of, for example, p-hydroxy-

and p-aminopropadrine. Will m-aminopropadrine, like m-hydroxypropadrine, take on greater sympathicotropic behaviour? Will complete sympathicotropic responses be possible with compounds such as,



e- Effect of Nuclear Methoxyl Group

The three monomethoxy isomers of β-phenethylamine have been synthesized by various workers dating from the synthesis of p-methoxy-β-phenethylamine by Mannich and Jacobsen (71) in 1910 up to about the time of Buck (72). Epstein, Gunn and Virden (73) determined the toxicity and pharmacological actions of p-methoxy- and m-methoxy-β-phenethylamine. They found that the effect of etherification of a phenolic hydroxyl group on the physiological activity of a particular compound is difficult to predict. However, in the particular group of compounds which they studied, there was reason to expect that such etherification would lead to a diminution of activity and an increase in toxicity. It seems interesting to note that these workers report that the para compound is considerably more toxic than the meta compound, which is the reverse in the case of unetherified hydroxy derivatives of β-phenethylamine. Hjort (39) taking most of the products prepared by Buck (72), studied the methoxyl substitution products of N-methylated β-phenethylamine and found a number of things:

1- In general, the introduction of methoxyl groups enhance the toxicity of β-phenethylmethylamine and diminishes its pressor effects.

2- All of these compounds have a variable amount of stimulating effect upon isolated segments of rabbit's uteri.

3- The circulatory effect is initiated by a brief depressor response in most instances in dogs. In cats the initial depressor response is more pronounced than in dogs.

4- Quantitatively the 2-methoxy compound has a low grade pressor effect after the initial depression. The 3- and 4- methoxy compounds are somewhat better pressor agents.

A table prepared from the data given by Hjort comparing the relative toxicity of the isomers and the unetherified derivatives is given on the following page.

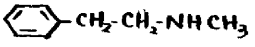
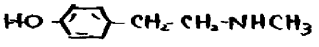
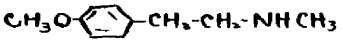
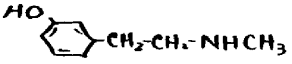
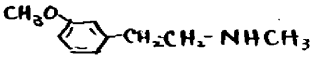
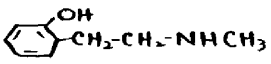
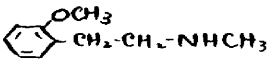
In the ethanolamine series, all the possible monomethoxy-isomers have been prepared by different groups of workers but no satisfactory pharmacological evaluations have been made.

In the ephedrine series, Koller (74) in 1926 found that p-methoxyephedrine acts like ephedrine but is weaker in action and that m-methoxy-p-hydroxyephedrine, when injected into rabbits, produced an indefinite effect on the circulation and a definite slowing of the respiration. Tiffeneau, Levy and Bayer

(75) synthesized p-methoxy-norhomo-ephedrine and found it to possess a greater pressor action than the parent compound, norphomo-ephedrine,

TABLE II

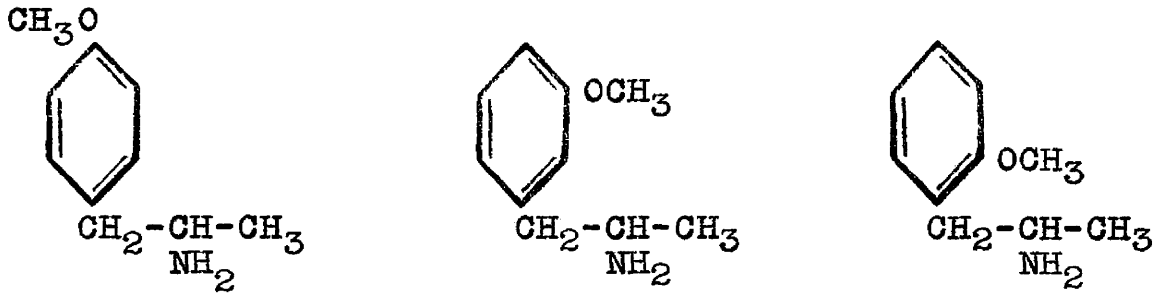
EFFECT OF METHYLATION ON TOXICITY

Compounds	Intraperitoneal LD 50 Mice
	200 mg./Kg.
	227
	165
	360
	173
	189
	173

In 1931, Hartung, Munch, Miller and Crossley (31) prepared several methoxyl compounds in the phenylpropanolamine series. They found that the ortho derivative was as active

but about three times as toxic as propadrine itself. The introduction of the para-methoxy group into propadrine increased the toxicity twofold and reduced the pressor activity to about one-half.

In 1938, Woodruff and Conger (34) became interested in the synthesis of methoxyl ring substituted derivatives of β-phenylisopropylamine for pharmacological study. They reported the preparation of the following compounds:



So far, their promise that "the pharmacological results will appear elsewhere" has not been journalistically fulfilled.

3,4-Dimethoxy-β-phenethylamine was synthesized first by Mannich and Jacobsen (71). Geesink and Jager (76) found that in the cat this compound causes 20% increase in arterial pressure. In 1913, Rosenmund synthesized 3,4-dimethoxyphenylethanolamine. A study of this compound was made by Kindler and Peschke (77). 3,4-Dimethoxyphenylisopropylamine was first prepared by Mannich and Jacobsen; Ide and Buck (78) reported a new synthesis of the same product in 1940. Outside of these synthetic work information concerning them is lacking.

Kondo, Shinozaki and Ishii (79) in 1928 and Buck (80) in 1932 synthesized 2,4-dimethoxy-β-phenethylamine. However, to date pharmacological data have not been reported. Hjort (39)

studied the N-methyl compounds of 2,4-dimethoxy derivatives which were prepared by Buck and found that it had a low grade of pressor effect after initial depression; and its toxicity to be about 1.4 times greater than unsubstituted parent compound. A more suitable determination of the effect of methylation can be derived by comparison between the 2,4-dihydroxy- and 2,4-dimethoxy derivatives of N-methyl-β-phenethylamine, but data for the free hydroxyl compound are not given. 2,4-Dimethoxyphenylpropanolamine was studied by Hartung, Munch, Miller and Crossley (31) and found to be as active as propadrine but more than three times as toxic.

Syntheses for 2,3-dimethoxy-β-phenethylamine have been reported by Haworth (81) in 1927 and by Buck (80). No pharmacological data appear. Hjort (39) determined the toxicity of 2,3-dimethoxy-N-methyl-β-phenethylamine and found it to be next in toxicity to 2,5-dimethoxy derivative, the latter being the most toxic of the dimethoxy isomers. Its pressor activity was found to be low.

In the 2,5-dimethoxy derivatives, Buck (80) and Baltzly and Buck (82,83) reported preparing 2,5-dimethoxy-β-phenethylamine, 2,5-dimethoxy-β-phenylpropanolamine, 2,5-dimethoxy-N-methyl-β-phenethylamine, 2,5-dimethoxy-β-phenylisopropylamine and 2,5-dimethoxyphenylethanolamine. Toxicity and pressor activity studies have been worked out only for the latter. Hjort found it to be a very promising pressor agent; however its merit is marred by its high toxicity, being about 1.9 times more toxic than the unmethylated 2,5-dihydroxy compound and about 1.7 times more toxic than the parent compound, β-

phenethylamine itself.

So far as it can be verified in the literature, none of the 2,6-dimethoxy derivatives has been synthesized. There is only one recorded instance of the mention of 3,5-dimethoxy derivative. In 1935, Bockmuhl, Ehrhart and Stein (84) were granted patent rights for their product, 3,5-dimethoxyphenyl-propanolamine. Search of literature for its physiological behaviour failed to disclose any further information. Such a compound having substitution on 3,5-positions should prove interesting.

The trimethoxyl substituted β-phenethylamines, especially the 3,4,5-trimethoxy derivative, form one of the most interesting groups of compounds in the annals of empiricism. The story begins with a plant called peyote or mescal.

Peyote or mescal is a small, fleshy, spineless cactus of the genus Lophophora williamsii (erroneously called Anhalonium lewinii)(85) which has been used for centuries by aboriginal Americans in connection with their religious rituals and as a magic plant believed to have the power of inducing supernatural visions.

The earliest description of the peyote plant is that of Hernandez (86), a learned Spanish physician sent in the sixteenth century by his sovereign, Philip II, to make a study of the resources of New Spain. He reported the plant to be:

> ...of nearly medium size sending forth no branches or leaves above ground, but with a certain wooliness adhering to it. Marvelous virtues are attributed to it by the Indians. It enables those eating it to foresee and prophesy such things, for instance, as whether on the following day the ene-

> my will make an attack upon them or whether the weather will continue favorable; or to discern who has stolen from them missing objects.....

Padre Sahagun (87) left many documental descriptions. The account is an entertaining one as written by Cairns (88):

> The good Padre Bernadino de Sahagun in the year 1529, at the age of thirty, arrived in Mexico or New Spain as it was affectionately called then to convert the harassed Aztecs to the gentle teachings of Saint Francis. The reverend father was a learned man and he left behind him when he died at the age of ninety-one valuable histories written in both the Spanish and the Aztec tongues. He gave in one of his histories a description of a curious feast of the Aztecs:
>
> > The first thing eaten at the party was a certain black mushroom, which they called nanacatl, which intoxicates and causes visions to be seen and even provoke sensuousness. These they ate with cacao (chocolate) syrup and when they began to feel the effect they began to dance; some sang; others wept because they were already intoxicated by the mushrooms; and some did not wish to sing but seated themselves in their rooms and remained there as though meditating. Some had visions that they were dying and shed tears; others that they were capturing prisoners in warfare; others that they were rich; others that they had many slaves; others that they had committed adultery and were to have their heads broken as a penalty; others that they had been guilty of a theft for which they were to be executed; and many other visions were seen by them. After the intoxication of the mushrooms had passed they conversed with one another about the visions which they had seen.

Botanists of modern times, finding these descriptions of the cactus and of the mushrooms, tried to identify the plant botanically and searched extensively; but it was not until 1915 that Safford (89) succeeded in identifying it with the mescal or peyote used by the American Indians of today (90,

91,92,93). The geographical distribution of peyote or mescal ranges from the southern border of Texas to Queretaro, Mexico. Thus the padre never laid eyes upon the cactus itself but saw only the dried mushroom-shaped buttons cut from the top of the cactus which were brought to the Aztecs by messengers consecrated to their tasks.

The peyote cult is widespread among the Indians. To the Indians the cult is a distinctly religious one (93) and the missionaries were opposed to peyote not so much on account of its physical effects on the Indians as because it was connected with the rituals of their religions and kept them from embracing Christianity.

In 1891 Mooney (94), who had assisted in the rites of some of the Indian tribes, brought a supply of buttons to Washington, D.C., which was handed over to Prentiss and Morgan (95). These investigators experimented on several young men and demonstrated for the first time the precise character of intoxication and the remarkable vision to which it gave rise. Shortly after their experiment three men of marked abilities, Weir Mitchell, William James and Havelock Ellis experimented with it on themselves.

Mitchell (96), the first of the three, took both an extract and tincture of the button. The experiment was highly successful. He described a stage of exhilaration and talkativeness, in which there is a dilatation of the pupils, flushing of the face, and a rather rapid pulse, followed by a condition which he describes as one of "deliciously languid ease and elat-

ed sense of superiority." Later color visions were seen, both with the eyes closed and opened, and a sleeplessness not accompanied, however, by any uneasy or restless feelings. One vision impressed him deeply:

> An edge of a huge cliff seemed to project over a gulf of unseen depth. My viewless enchanter set on the brink a huge bird claw of stone. Above from the stem or leg, hung a fragment of the same stuff. This began to unroll and float out to a distance which seemed to me to represent Time as well as immensity of Space. Here were miles of ripped purples, half transparent, and of ineffable beauty. Now and then soft golden clouds floated from these folds, or a great shimmer went over the whole of the rolling purples, and things like green birds, fell from it, fluttering down into the gulf below....

After experimenting upon himself, Mitchell sent a supply to William James. James' experience (88) was an unhappy one and he wrote to his brother Henry:

> I had two days spoiled by a psychological experiment with mescal....Weir Mitchell sent me some to try. He had himself been in fairyland! It gives the most glorious visions of color; every object thought of appears in a jeweled splendor unknown to the natural world. It disturbs the stomach somewhat, but that according to W.M., was a cheap price, etc. I took one bud but three days ago, was violently sick for twenty-four hours....I will take the visions on trust!

In the spring of 1897, Havelock Ellis (94) was able to obtain a small sample in London, and on Good Friday of the same year he prepared a decoction of three buttons and drank it at intervals between 2:30 and 4:30 P.M. The first symptom observed during the afternoon was a "certain consciousness of energy and intellectual power." Unlike those of James, Ellis' visionary experiences were eminently successful. He wrote:

> The appearance of visions with closed eyes was very gradual. At first there was merely a vague play of light and shade which suggested pictures, but never made them....in the course of the evening, they became distinct, but still indescribable--mostly a vast field of golden jewels studded with red and green stones, ever changing. This moment was, perhaps, the most delightful of the experience, for at the same time the air around me seemed to be flushed with vague perfume--producing with the visions a delicious effect--and all discomfort had vanished.... I would see thick, glorious fields of jewels, solitary or clustered, sometimes brilliant and sparkling, sometimes with a dull rich glow....

Ellis tried to sleep that evening but did not have the faintest desire for sleep. About 3:30 A.M. he was able to settle himself to peaceful and dreamless sleep, awaking at the usual hour with no sense of fatigue nor other unpleasant reminiscence. His eyes seemed unusually sensitive to color especially to blue and violet after the experience.

Some time later he again put himself under the influence of mescal to test the effect of music upon the visions. The chief object of the tests was to ascertain how far a desire on the composer's part to suggest definite imagery would affect his visions. In about half the cases there were no resemblances; in the other half there were distinct resemblances, which were sometimes very remarkable:

> This was especially the case with Schumann's music, for example...."The Prophet Bird" called up vividly a sense of atmosphere and of brilliant feathery bird-like forms passing to and fro, "A Flower Piece" provoked constant and persistent images of vegetation covered by glittering spangles and jewels. In every case my description was, of course, given before I knew the name of the piece....

Since the experiments of the early investigators, the properties of the drug have been further analyzed. The first to study the chemical properties of peyote was Lewin (97) in 1888. A chemical analysis was made by Ewell (98). Heffter (99) investigated the cactus alkaloids most completely and seven bases are described: anhaline, mescaline, pellotine, anhalonidine, anhalonine, anhalamine and lophophorine. Mogilewa (100) found that these have about the same physiological activity and are closely related chemically. Spath (101) elucidated the structure and synthesized mescaline by a method which showed that it is 3,4,5-trimethoxy-β-phenethylamine. Reutter (102) described the physiological effects of mescal buttons used by the natives of Mexico and attributed these effects solely to the alkaloid, mescaline. Sollman (103) states that the most important alkaloid of the cactus Lophophora williamsii is mescaline which produces very peculiar psychological disorientations with hallucinations of the special senses, particularly flashes and lines of ever-changing brilliant colors. Dixon (104) found that they appear the same in both eyes and are therefore central. A psychologic study of mescaline hallucinations has been made by Knauer and Maloney in 1913 (105). Guttmann and Maclay (106) who administered small doses of the synthetic alkaloid orally to psychotic patients classify the effects as depersonization (confusion of personality), derealization (unreality of environment) and hallucinations similar to schizophrenia. Grace (107) observed that mescaline and its related compounds produce a number of

other effects, including fall of blood pressure which can be prevented by vagotomy or atropine, motor paralysis by depression of the central nervous system and death by respiratory failure.

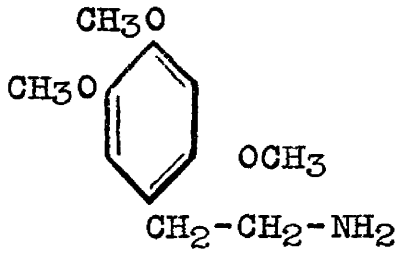
On the matter of effect on blood pressure, Raymond-Hamet (108) found that mescaline sulfate, when injected into the dog (2 to 8 mg per Kg), generally causes a fall in blood pressure; that larger doses (20 mg per Kg) always cause a fall; and that moderate doses (8 mg per Kg) markedly inhibit the pressor effect of epinephrine without affecting its accelerating effect on cardiac rate. De Nito (109) found that in dog 40 mg per Kg slowed the heart and caused a fall in blood pressure which was not affected by vagotomy or atropinization. Geesink and Jager (76) found that mescaline does not have any effect on arterial pressure. Incidentally, these latter workers found that 3,5-dimethoxy-β-phenethylamine increased the arterial pressure by 20%.

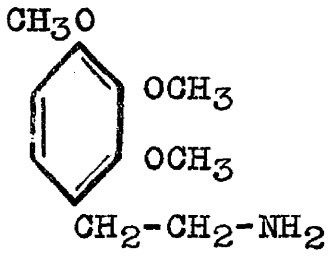
Allksandrovski, Babskii and Kryazhev (110) extrapolated the results that they obtained in the study of changes in the motor reflexes of dogs following a single intoxication with mescaline and conjectured that "in accordance with the psychopathology of mescaline poisoning in man the experimental material leads to the conclusion that the action of the poison on the visual centers is selective."

In view of the finding of Blaschko (111) that ephedrine acts as an inhibitor of amine oxidase and that other derivatives of β-phenylethylisopropylamine have a like action, it would not be too bold to express the view that the report of

Richter (112) was expected, namely that ephedrine, benzedrine, ℓ-phenylisopropylmethylamine are excreted unchanged. Since amines of the general type, $R\text{-}CH_2\text{-}NH_2$, are rapidly oxidized in man, it is surprising to note the report of Richter in the same article who observed that mescaline is also excreted unchanged; and, what is more, he measured their rates of excretion.

Recently the two isomers of mescaline were synthesized by Slotta and Heller (113). These isomers are:





Their concluding note, "The physiological action of the amines prepared will be described later by Hesse and Lange," unfortunately did not come to realization as far as literature search revealed. However, Jansen (114) working on the 2,4,5-trimethoxy isomer found that comparative experiments on frogs and cats showed that the pharmacologic al action of the 2,4,5-trimethoxy isomer agree to a large extent with that of mescaline. The 2,4,5-trimethoxy isomer however had more unpleasant secondary effects (nausea) and did not bring about the euphoristic state caused by mescaline.

Two other compounds bearing the trimethoxyl groups have been synthesized. Hinsberg (46) prepared 2,3,4-trimethoxyphenylethanolamine; Kindler and Peschke (77) reported the

preparation of 3,4,5-trimethoxyphenylethanolamine. Pharmacological properties of both of these compounds are still unknown.

The foregoing survey of biological literature is summarized in a tabular comparative form especially between the nuclear substituted hydroxy compounds and its methyl ether wherever possible.

TABLE III

COMPARISON OF NUCLEAR HYDROXYL AND METHOXYL SUBSTITUTED PRESSOR AMINES

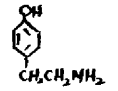
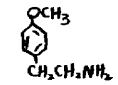
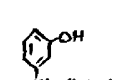
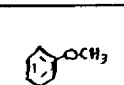
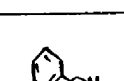
	SYNTHESIS		PHARMACOLOGY			
	Author, Year	Ref.	Author, Year	Ref.	Toxicity	Pressor Act.
			Barger + Dale, 1910 Chen, Wu + Henriksen, 1929	13 26	MLD 40-50 mg./Kg. I.V. Rabbits	$\frac{1}{350}$-$\frac{1}{233}$ of Epinephrine
			Barger + Dale, 1910	13	MLD 800 mg/Kg. IP Mice	5 times as active as β-phenethylamine $\frac{1}{70}$ of Epinephrine
	Mannich + Jacobsen, 1910 Kondo, Shiozaki + Ishii 1929 Kondo + Tanaka, 1932	71 79 153	Epstein, Gunn + Virden, 1932	73	MLD 180 mg/Kg IP Mice	$\frac{1}{300}$ of Epinephrine
			Barger + Dale, 1910	13		Same as p-hydroxy β-phenethylamine (Tyramine)
	Helfer, 1924 Buck, 1932	152 80	Epstein, Gunn + Virden, 1932	73	MLD 230 mg/Kg IP Mice	$\frac{1}{300}$ of Epinephrine
	Kondo, Shiozaki + Ishii 1929 Buck, 1932	79 80	Barger + Dale, 1910	13		$\frac{1}{5}$ of Tyramine

TABLE III

(continued)

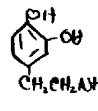
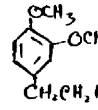
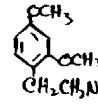
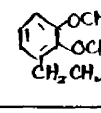
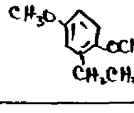
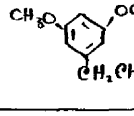
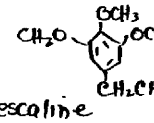
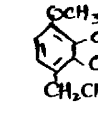
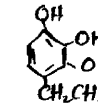
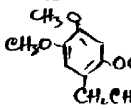
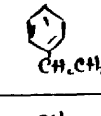
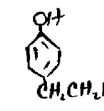
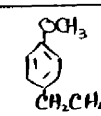
Compound	SYNTHESIS		PHARMACOLOGY			
	Author, Year	Ref.	Author, Year	Ref.	Toxicity	Pressor Act.
			Barger + Dale, 1910	13		Twice as active as tyramine.
	Kindler, 1931 Hahn + Schales, 1934 Julian + Sturgis, 1935	156 157 158	Epstein, Gunn + Virden, 1932	73	MLD 420 mg./Kg. I.P. Mice	Slight transient pressor followed by a prolonged depressor action.
	Kondo, Shiozaki + Ishii, 1929 Buck, 1932	79 80				
	Haworth, 1927 Kondo, Shiozaki + Ishii, 1929 Buck, 1932	81 79 80				
	Kondo, Shiozaki + Ishii, 1929 Buck, 1932 Battzly + Buck, 1940	79 80 82				
	Slotta + Heller, 1930	113				
 Mescaline	Spath, 1919 Slotta + Heller, 1930 Slotta + Szyszka, 1931	101 113 159	Mogilewo, 1903 Heffter, 1896 Reutter, 1927 Raymond-Hamet, 1941 Grace, 1934	100 99 102 108 107	MLD 500-600 mg./Kg. I.P. Mice (Grace)	Both pressor and depressor. See text.
	Slotta + Heller, 1930	113				
			Barger + Dale	13		Twice as active as tyramine
	Jansen, 1929	160	Jansen, 1931	114	Similar to Mescaline	Similar to Mescaline but no color visions
			Barger + Dale, 1910	13	LD 50 203 mg./Kg. I.P. Mice	>160 mm. Hg. on Anesthet. dog. Duration: 5 mins
			Barger + Dale, 1910 Chen, Wu + Henriksen, 1929 Alles, 1933 Hjort, 1934 Gunn, 1939	13 26 51 39 148	LD 50 227 mg./Kg. I.P. Mice	>130 mm. Hg. on Anesthet. dog. Duration: 5 min
			Hjort, 1934	39	LD 50 165 mg./Kg. I.P. Mice	Initial depressor, <30 mm. — ¼ min. Then pressor, >130 mm. — 7½ mins

TABLE III
(continued)

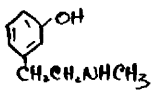
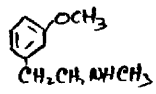
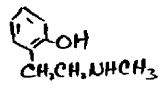
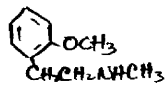
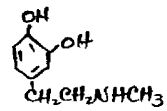
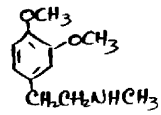
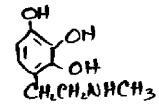
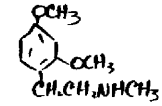
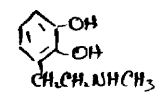
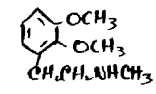
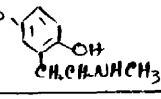
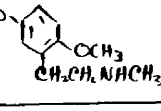
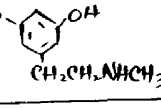
	SYNTHESIS		PHARMACOLOGY			
	Author, Year	Ref.	Author, Year	Ref.	Toxicity	Pressor Act.
	Buck, 1932	80	Hjort, 1934	39	LD 50 360 mg./Kg. I.P. Mice	>120 mm —— 5 mins.
	"	"	"	"	LD 50 173 mg./Kg. I.P. Mice	>130 mm —— 4 mins.
	"	"	"	"	LD 50 189 mg./Kg. I.P. Mice	>110 mm. — 6 mins.
	"	"	"	"	LD 50 173 mg./Kg. I.P. Mice	Initial depressor, <42 mm — ½ min Then pressor, >40 mm —— 5 mins.
	Pyman, 1909 Buck, 1930	165 164	Tainter, 1929 Hjort, 1934 Giles, 1933	50 39 51	LD 50 627 mg./Kg. I.P. Mice	>104 — 5 mins
	Buck, 1932	164	Hjort, 1934	39	LD 50 322 mg./Kg. I.P. Mice	Initial depressor, <50 mm — 1 min Then pressor, >30 mm — 5 mins.
	Mentioned by Buck, 1932	80	Mentioned by Buck, 1932 Hjort, 1934	39	Not investigated	Not investigated
	Buck, 1932	80	Hjort, 1934	39	LD 50 146 mg./Kg. I.P. Mice	Initial depressor <16 mm — ½ min. Then pressor >46 mm —— ½ min.
	"	"	"	"	LD 50 318 mg./Kg. I.P. Mice	>104 mm — 6 mins.
	"	"	"	"	LD 50 137 mg./Kg. I.P. Mice	Initial depressor, <80 mm — 3 mins Then pressor, >20 mm — 3 mins
	"	"	"	"	LD 50 234 mg./Kg. I.P. Mice	>104 mm. — 9 mins
	"	"	"	"	LD 50 122 mg./Kg. I.P. Mice	>94 mm. — 25 mins
	Mentioned by Buck, 1932	80	Mentioned by Hjort, 1934	39	Not investigated	Not investigated

TABLE III
(continued)

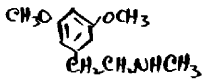
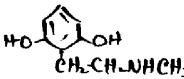
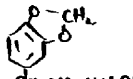
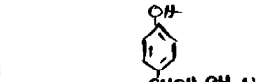
	SYNTHESIS		PHARMACOLOGY			
	Author, Year	Ref.	Author, Year	Ref.	Toxicity	Pressor Act.
	Mentioned by Bock, 1932	80	Mentioned by Hjort, 1934	39	Not investigated	Not investigated
	"	"	"	"	"	"
	"	"	"	"	"	"
			Hjort, 1934	39	LD 50 215mg./Kg. I.P. Mice	Initial depressor <4mm — $\frac{1}{2}$min Then pressor, >110 mm — 3min
 l-Epinephrine	Stolz, 1904 Dakin, 1905	186 179	"	"	LD 50 44 mg./Kg. I.P. Mice	>120mm — 3mins
 d-Epinephrine	" "	" "	"	"	LD 50 5.7mg./Kg. I.P. Mice	>120mm — 3mins.
 "Synephrine"	Ehrisman, 1927 Lasch, 1927	182 183	Ehrisman, 1927 Lasch, 1927 Tainter & Seidenfeld, 1930	182 183 184	MLD 400mg./Kg. Mice (Lasch)	$\frac{1}{116}$ of Epinephrine (Tainter)
			Chen, Wu & Henriksen, 1929	26	MLD. 100mg./Kg. I.V. Rabbit	$\frac{1}{700}$ of Epinephrine
 "Neo-synephrine"			Tainter, 1932 Tainter & Stockton, 1933	151 150	Margin of safety 8 times that of Epinephrine in equipressor doses.	$\frac{1}{9}$ of Epinephrine
 l-Ephedrine	Fourneau, 1904 Nagai, 1911 Spath & Göring	167 168 169	Chen & Schmidt, 1930 Hirose, 1915	172 171	MLD 60mg./Kg. White rabbit	>100mm — 15-25 Mins
 d-Ephedrine	" " "	" " "	" "	" "	MLD 80mg./Kg. White rabbit	>100 mm — 15-25 mins
			Schaumann, 1931	33	Least toxic of the monohydroxy series.	Not adequately studied
	Kohler, 1926	74	Kohler, 1926	74		Similar to Ephedrine but weaker

TABLE III
(continued)

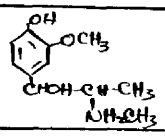
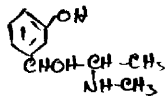
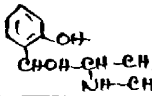
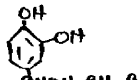
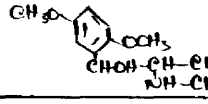
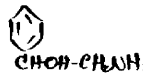
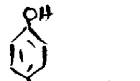
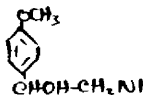
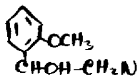
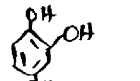
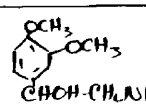
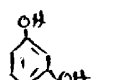
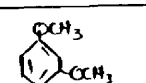
	SYNTHESIS		PHARMACOLOGY			
	Author, Year	Ref.	Author, Year	Ref.	Toxicity	Pressor Act.
	Kohler, 1926	74	Kohler, 1926	74		Indefinite effect to rabbits
			Schaumann, 1931	33		Best pressor agent of the monohydroxy series.
			"	"		Least active of the monohydroxy series.
			Schaumann, 1931 Tainter, 1933	33 46		$\frac{1}{41}$ of Epinephrine
	Baltzly & Buck, 1940	82				
	Kolshorn, 1904 Rosenmund, 1912	162 154	Barger & Dale, 1910 Hirose, 1915 Alles, 1927 Chen, Du & Henriksen, 1929	13 171 178 26	MLD 80 mg./Kg. I.V. Rabbits	$\frac{1}{350}$ of Epinephrine
	Tutin, Caton & Henn, 1909 Boruttau, 1912 Mannich & Thiele, 1915	163 38 177	Barger & Dale, 1910	13		$\frac{1}{5}$ of Tyramine
	Rosenmund, 1913 Mannich & Thiele, 1915 Kindler & Peschke, 1931 Reichert & Koch, 1935	154 177 77 173				
	Kondo & Tanaka, 1930 Buck, 1933 Reichert & Koch, 1935	156 61 173				
 "Afferenol"	Rosenmund, 1913 Hirsberg, 1923 Kindler & Peschke, 1931	154 46 77	Barger & Dale, 1910	13		1.4 times as active as Epinephrine
	Rosenmund, 1913 Kindler & Peschke, 1931 Reichert & Koch, 1935	154 77 173				
	Boruttau, 1912	38	Boruttau, 1912	38		Only a slight effect.
	Reichert & Koch, 1935	173				

TABLE III

(continued)

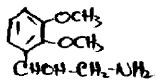
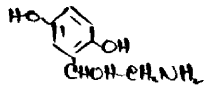
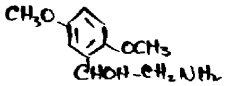
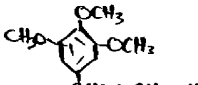
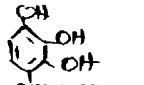
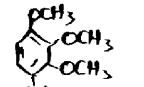
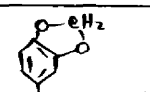
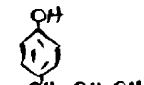
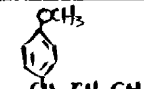
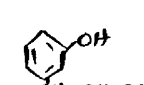
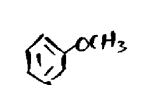
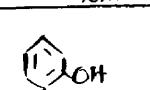
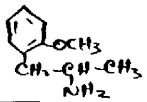
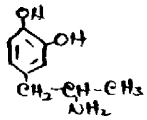
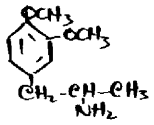
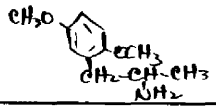
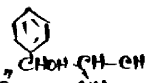
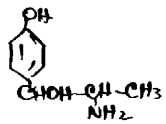
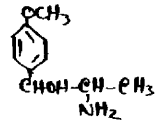
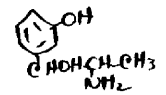
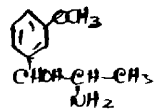
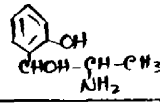
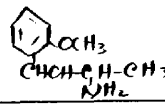
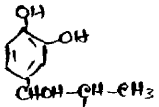
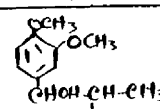
	SYNTHESIS		PHARMACOLOGY			
	Author, Year	Ref.	Author, Year	Ref.	Toxicity	Pressor Act.
	Buck, 1932	80				
	Boruttau, 1912	38	Boruttau, 1912	38		Greater pressor effect than 2,4-isomer.
	Battzly & Buck, 1940	82				
	Kindler & Peschke, 1931	77				
	Hirsberg, 1923 German patents, 1926	46 176				
	" "	" "				
	German patents, 1911 Kindler & Peschke, 1931 Alles, 1933 Reichert & Koch, 1935	174 77 175 173				
 Amphetamine	Hey, 1930 Alles, 1932	185 161	Alles, 1933 Hartung & Munch, 1931	51 186	MLD 25 mg./kg. I.U. Rabbits (Hartung)	$\frac{1}{100}$ to $\frac{1}{200}$ of Epinephrine (Alles)
	Mannich & Jacobsen, 1910 Alles, 1932 Woodruff & Conger, 1938	71 161 34	Barbour, 1916 Hasama, 1930 Alles, 1933	181 51 188	MLD 2200 mg./kg. Subcutan. Mouse (~~Hartung~~)	$\frac{1}{50}$ – $\frac{1}{100}$ of Epinephrine (Alles)
	Mannich & Jacobsen, 1910 Woodruff & Conger, 1938	71 34	Geesink & Jager, 1939	76		20% increase in arterial pressure
	Woodruff & Conger, 1938	34	Woodruff & Conger: "The pharmacological results will appear elsewhere."			
	"	"	"	"	"	"
	"	"	"	"	"	"

TABLE III
(continued)

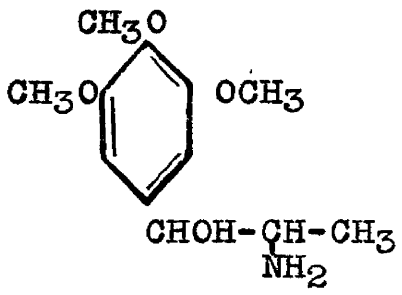
	SYNTHESIS		PHARMACOLOGY			
	Author, Year	Ref.	Author, Year	Ref.	Toxicity	Pressor Act.
	Woodruff & Conger, 1938	34	Woodruff & Conger: "The pharmacological results will appear elsewhere."			
	Mannich & Jacobsen, 1910 Alles, 1932	71 161	Alles, 1933	51	Data not significant. Insufficient sample	$\frac{1}{50}$ of Epinephrine
	Mannich & Jacobsen, 1910 Ide & Buck, 1940	71 78				
	Baltzly & Buck, 1940	82				
"Propadrine" 	Raber & Hallensleben, 1910 Catlies, Nagai & Eberhard, 1917	180 181	Hartung & Munch, 1929 Hartung, Munch, Miller & Crossley, 1931	49 31	MLD 75mg./Kg. I.V. Rabbit	dl-form equals l-ephedrine
	Hartung, Munch, Miller & Crossley, 1931	31	Hartung, Munch, Miller & Crossley, 1931	31	MLD 100-125mg/kg. I.V. Rabbit	1.5 times as active as propadrine
	"	"	"		MLD 35mg./Kg. I.V. Rabbit	$\frac{1}{2}$ of propadrine
	"	"	" Tainter, 1932	 151	MLD 16mg./Kg. I.V. Rabbit	3 times as active as propadrine
	Forthcoming					
	Hartung, Munch, Miller & Crossley, 1931	31	Hartung, Munch, Miller & Crossley, 1931	31	MLD 40 mg./Kg. I.V. Rabbit	Less active than propadrine
	"	"	"	"	MLD 25mg./Kg. I.V. Rabbit	Same as propadrine
	"	"	" Tainter, 1931	 149	MLD 11mg./Kg. I.V. Rabbit	12 times as active as propadrine
	Now being reported					

AIM OF RESEARCH

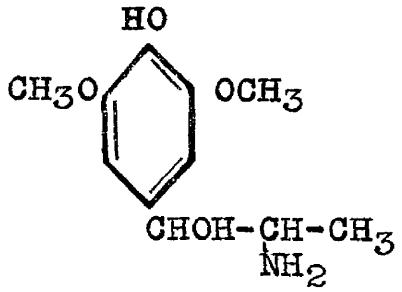
β-Phenethylamine has been shown to be an active pressor agent. Structurally, mescaline bears the same skeleton and consequently it would not be too much to expect mescaline at least to exert some pressor activity. Yet, mescaline apparently does not. Could this be because of the presence of three methoxyl groups vicinal to each other on the aromatic ring? Does the presence of these methoxyl groups influence the molecule to such an extent as to prevent amine oxidase from attacking the $AR-CH_2-NH_2$ linkage, to annihilate the pressor activity which is the intrinsic property of the β-phenethylamine structure, to direct the physiological activity selectively to visual centers, and to produce a happy state of euphoria?

If such changes can be derived, what might be the resultant physiological characteristics of a molecule which combines the 3,4,5-trimethoxyl moiety with that of a molecular moiety known to be less toxic, orally active and a pressor? Would such a compound produce in responsive tissues a sense of universal well-being and a colorful perspective?

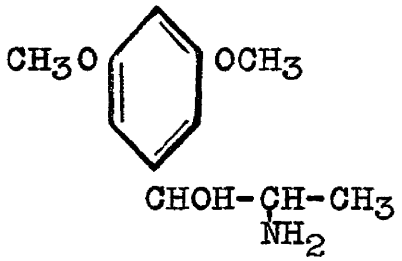
In sincere hopes of finding answers to some of these questions especially the answer to the relation between nature of response and the presence and position of the methoxyl groups on the nucleus, syntheses of four propadrine derivatives were undertaken: 3,4,5-trimethoxy-, 3,4-dimethoxy-, 3,5-dimethoxy- and 3,5-dimethoxy-4-hydroxypropadrines.



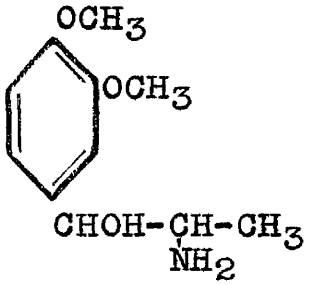
3,4,5-Trimethoxypropadrine



3,5-Dimethoxy-4-hydroxypropadrine



3,5-Dimethoxypropadrine

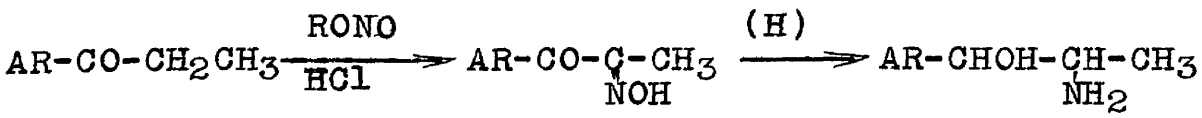


3,4-Dimethoxypropadrine

By the study of these compounds it is hoped that sufficient data may be obtained to enable one to understand better, even in a small way, the problem of biochemorphology.....the relation between chemical structure and physiological activity.

SURVEY OF AVAILABLE METHODS OF APPROACH

It is known that ketones of the type AR-CO-CH_2-R may readily be nitrosated and the product catalytically reduced to the corresponding amino alcohols:

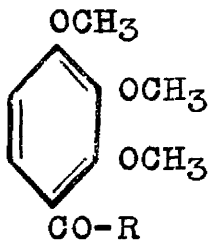


This scheme of reaction has been successfully applied to alkyl, hydroxyl and methoxyl ring substituted derivatives of phenylpropanolamines (31,52,115). Since both the nitrosation and catalytic reduction reactions have given excellent results, it was proposed to follow this plan in this study.

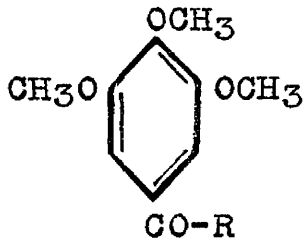
The bulk of the problem lay in the synthesis of the appropriate ketones.

3,4,5-Trimethoxy- and 3,5-Dimethoxy-4-hydroxypropiophenones

At the time Bogert and Isham (116) first began their work on ketones derived from trimethylgallic acid, they found that Nencki (117) and Mannich and Hahn (118) had obtained ketones of the Type I by the application of Friedel-Crafts reaction to trimethylpyrogallol, but of the isomeric Type II only one reference was found in the literature. This reference was by Mauthner (119) who had prepared the 3,4,5-trimethoxyacetophenone from trimethylgallic aldehyde by the action of diazomethane.



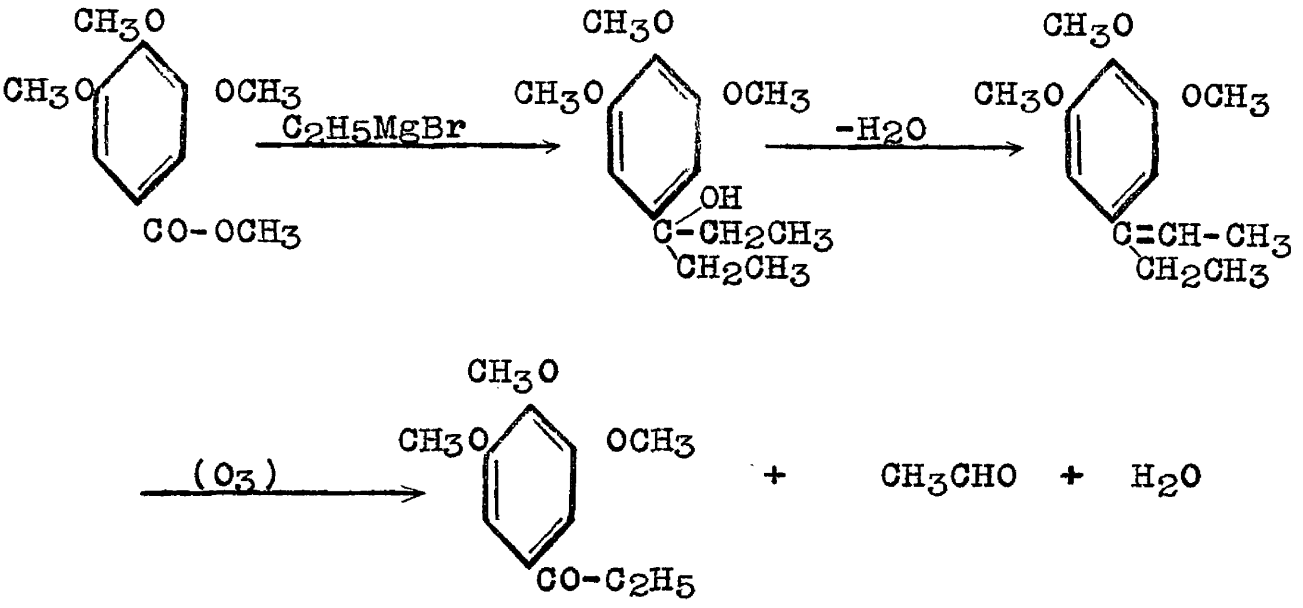
Type I



Type II

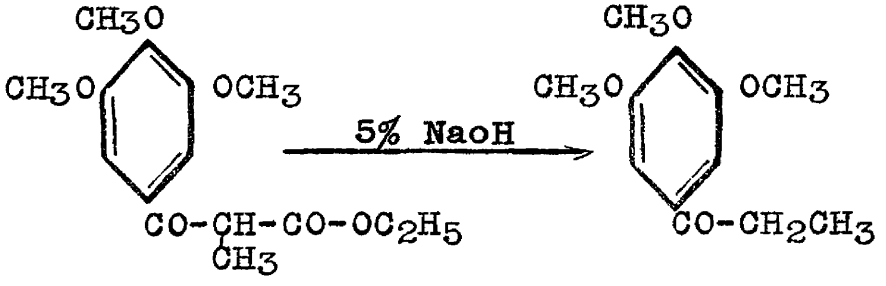
In 1914 Bogert and Isham succeeded in preparing the compound described by Mauthner and a number of others of this type (Type II) by taking the olefins secured in their Grignard

reactions and treating them with ozone according to Harries' method:

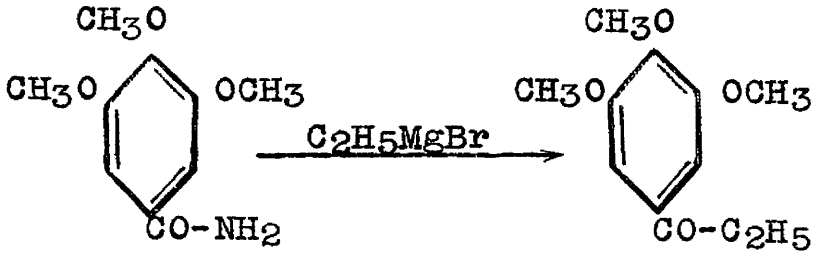


Mauthner in 1925 (120) prepared the same propiophenone derivative by another method.

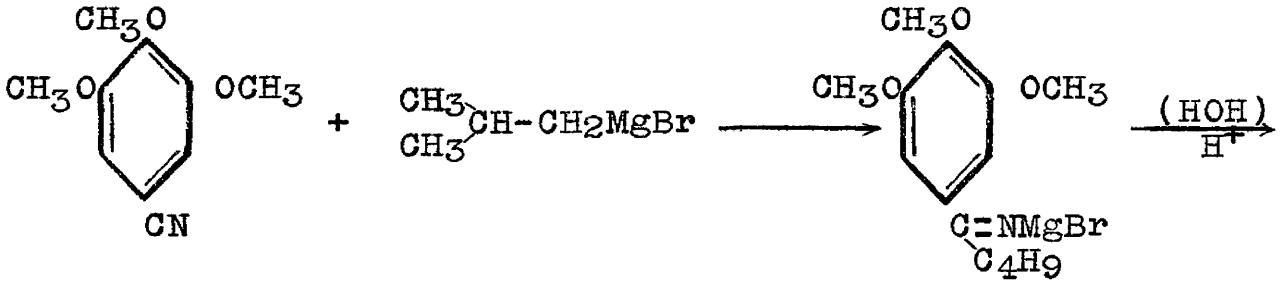
In 1936 Asahina (121) prepared it in this manner:

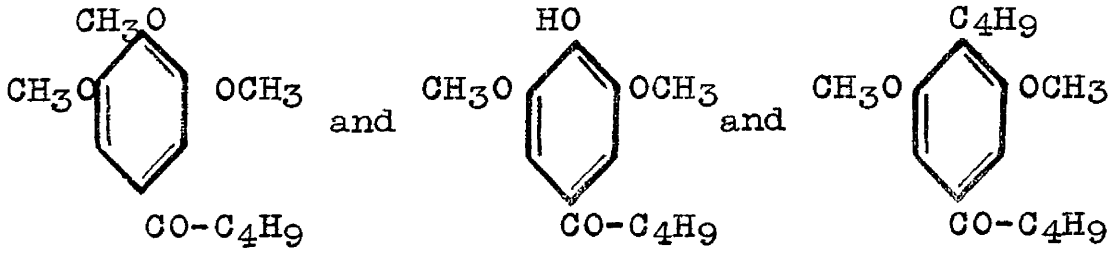


Couturier in 1938 (122) carried out Grignard reactions on hydroxy and alkoxy benzamides and obtained ketones. He synthesized 3,4,5-trimethoxypropiophenone in this manner:



A year later Haller and Schaffer (123) investigated the course of reaction between isobutylmagnesium bromide and 3,4,5-trimethoxybenzonitrile at the refluxing temperature of toluene. In addition to the expected isobutyl ketone, they obtained a phenolic ketone and a second neutral ketone,





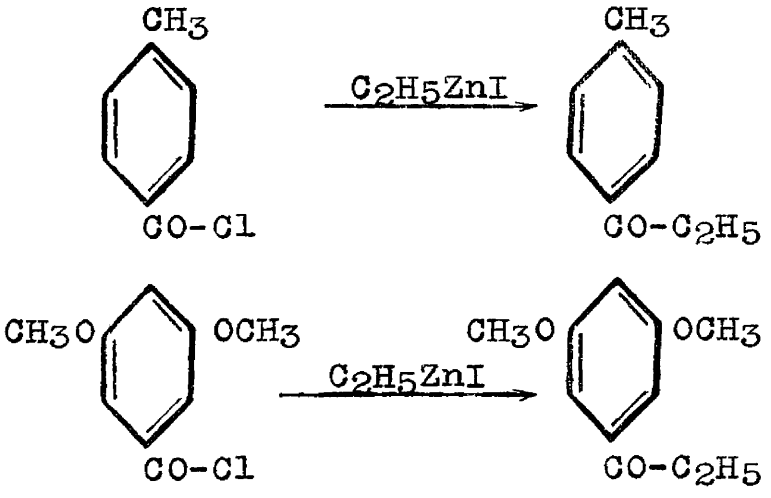
In 1942 Hurd and Winberg (124), at the suggestion of Haller and Schaffer, continued the study of the behaviour of the reaction between 3,4,5-trimethoxybenzonitrile and Grignard reagents and attempted to find the conditions which preferentially tended to give one of the products over the other. They found that by increasing the molar ratio of the Grignard reagent from

two and one-half to fourfold excess and the reaction time from three to five hours at the refluxing temperature of toluene, the yield of hydrolysis products may be greatly increased at the expense of the trimethoxy ketone. However, at 40° and with the longer reaction period cleavage of the ether linkage does not occur, the only product being the trimethoxy ketone.

Hickenbottom (125) describes a method of preparation of ketones using zinc alkyl halides on acyl halides,

$$R\text{-}CO\text{-}Cl + RZnX \longrightarrow R\text{-}CO\text{-}R + ZnXCl$$

A reaction of this type has been applied to the synthesis of aralkyl ketones by Mauthner (126),

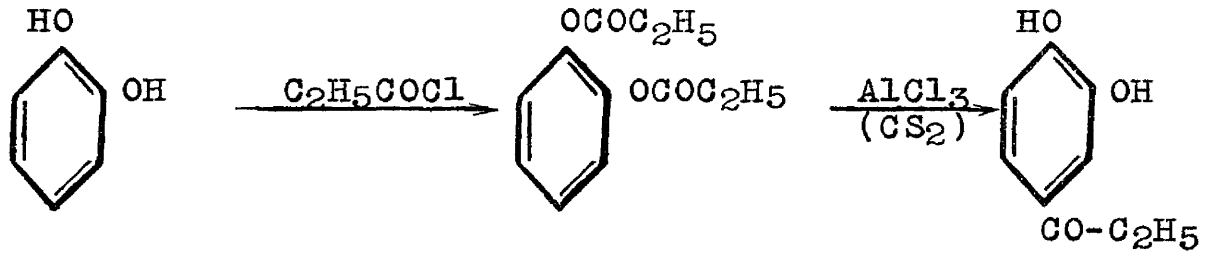


Of these available methods, the method finally adopted for the synthesis of 3,4,5-trimethoxypropiophenone was the method of Haller and Schaffer, because in addition to the trimethoxyl derivative 3,5-dimethoxy-4-hydroxypropiophenone was also desired. The method using zinc alkyl halide appeared to be a promising one; but due to the difficulty encountered in obtaining the acid chloride in pure form, it was laid aside temporarily

with the hope of developing the method in the event of failure of the method chosen first.

3,4-Dimethoxypropiophenone

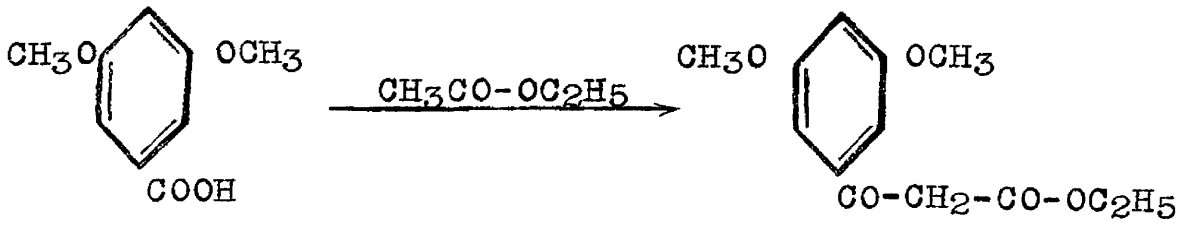
The method adopted was the one used by Rosenmund and Lohfert (127) who prepared propionyl catechol by Fries rearrangement of the catechol dipropionate. The technique of the rearrangement pursued was that used by Miller, Hartung, Rock and Crossley (189),

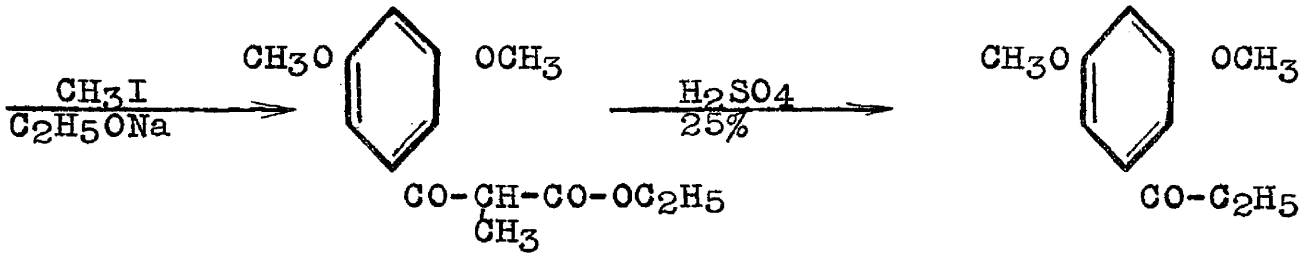


The propionyl catechol was methylated by the usual method of methylation using dimethyl sulfate and alkali.

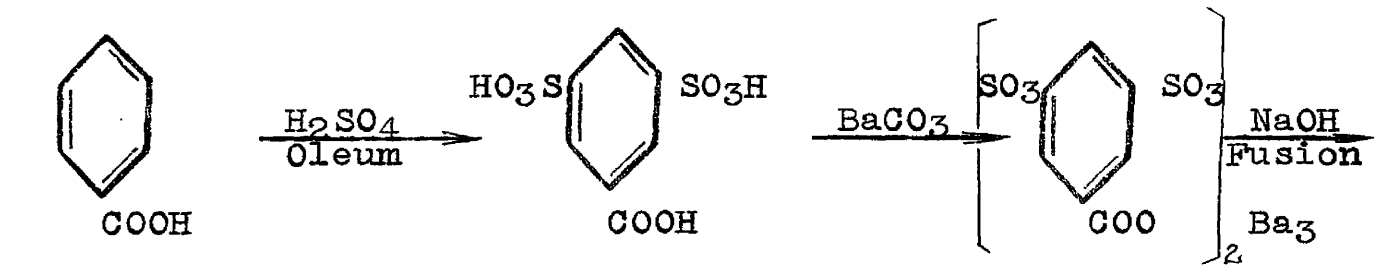
3,5-Dimethoxypropiophenone

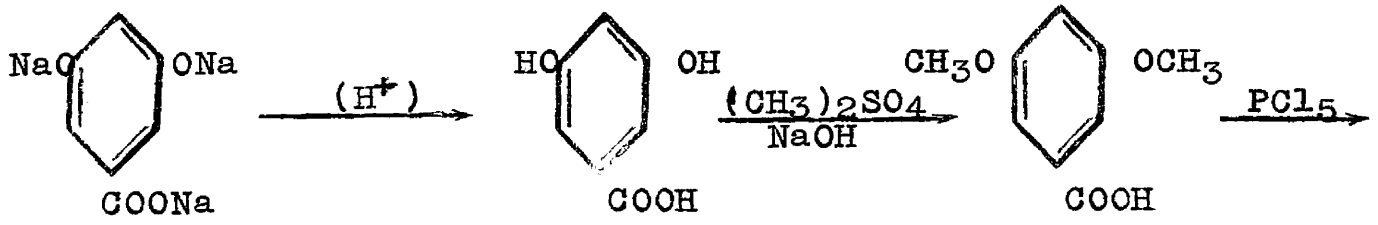
Mauthner in 1924 (128) had prepared 3,5-dimethoxypropiophenone by starting with 3,5-dimethoxybenzoic acid in the following manner:

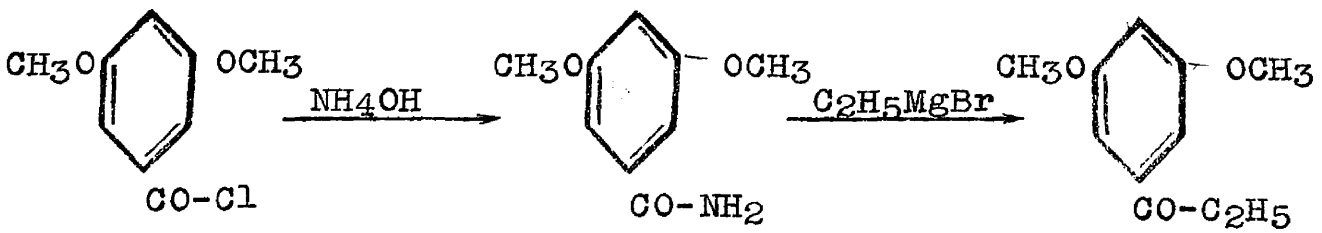




However, due to lack of material that Mauthner used for his initial reaction, the method followed in the Laboratory was that of Suter and Weston (129). These workers began their series of reactions with a more elementary product, benzoic acid. The reactions are







EXPERIMENTAL

The experimental portion consisted of three general divisions and have been empirically developed in the following order:

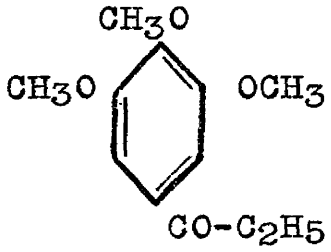
I. Synthesis of Ketones

II. Nitrosation of Ketones

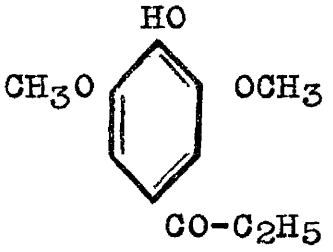
III. Catalytic Reduction to Amino Alcohols

I. Synthesis of Ketones

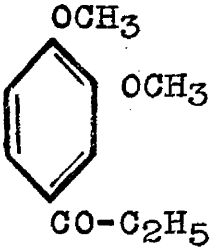
Four aralkoxy ketones were prepared. They were



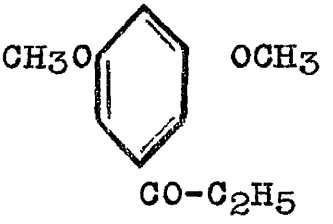
3,4,5-Trimethoxypropiophenone



3,5-Dimethoxy-4-hydroxypropiophenone



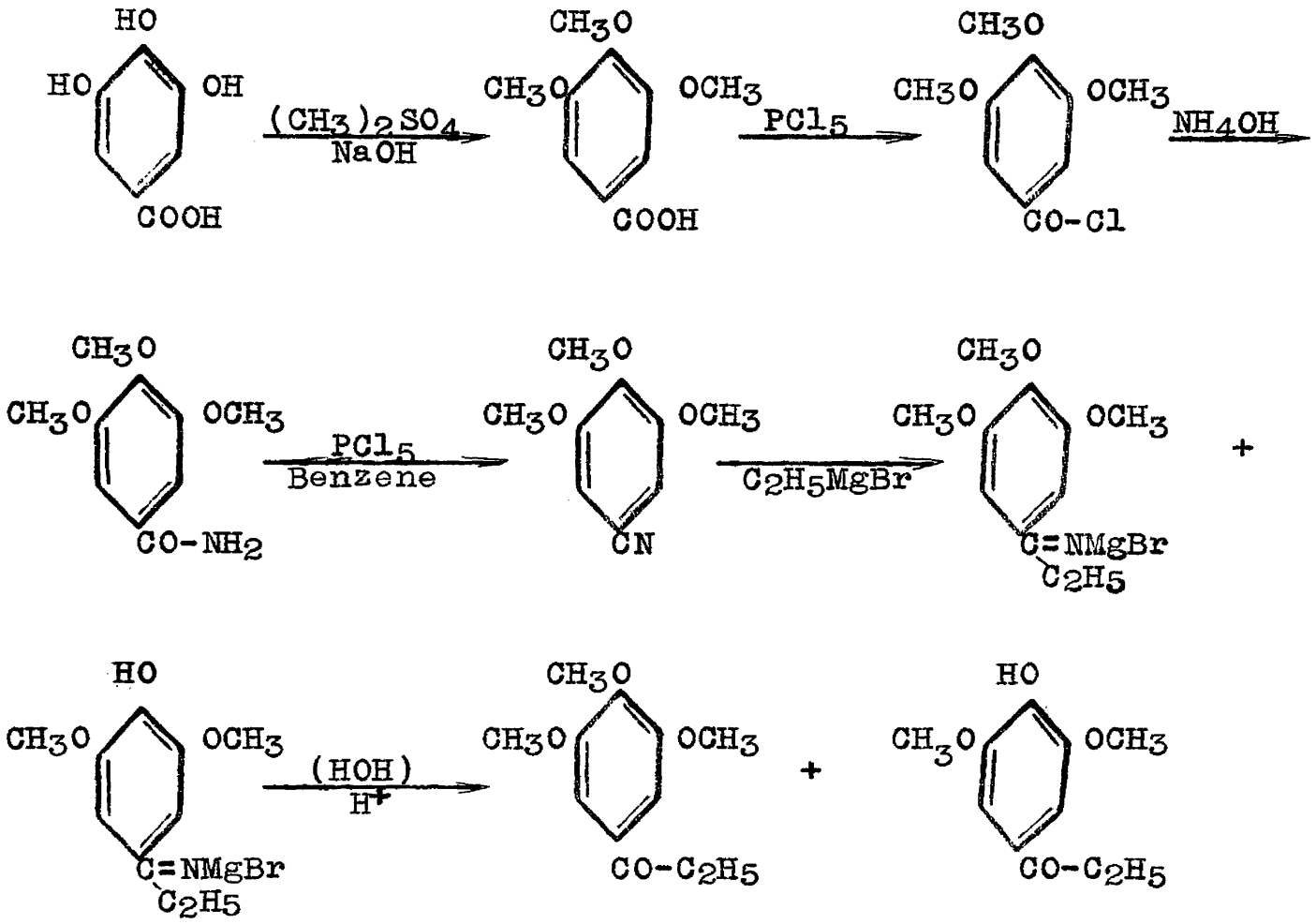
3,4-Dimethoxypropiophenone



3,5-Dimethoxypropiophenone

3,4,5-Trimethoxy- and 3,5-dimethoxy-4-hydroxypropiophenone were prepared from gallic acid through the following series of

reactions:



Trimethylgallic acid

Gallic acid was methylated by following precisely the method described by Mauthner (130).

To a cold solution of 80 g. (2 moles) of sodium hydroxide dissolved in 500 cc. of water in a three-necked one-liter flask equipped with a mechanical stirrer, a reflux condenser and a stopper, 50 g. (.266 mole) of gallic acid, Eastman technical grade, was slowly added over a period of fifteen minutes with continuous stirring until all the acid had dissolved. The solu-

tion darkened due to oxidation; sodium bisulfite has been recommended to prevent oxidation during methylation (131). After the final addition of the acid, the stopper was replaced by a dropping funnel.

Dimethyl sulfate, 89 g. (.71 mole), was added dropwise and the flask continuously stirred for fifteen minutes before the addition of a second portion. Heat was evolved in the reaction; the flask was cooled by means of a water-ice bath in order that the temperature did not rise above 30-35°. A second portion of 89 g. of dimethyl sulfate was then added as previously described. During the second addition the temperature was allowed to rise to 40-45° and stirred for about thirty minutes longer.

The contents of the reaction flask were refluxed for two hours with continuous agitation. In order to saponify the small amount of methyl ester which was produced, a solution of 20 g. of sodium hydroxide in 30 cc. of water was added and refluxing continued gently for two additional hours.

The reaction mixture was cooled and the trimethylgallic acid was forced to precipitate by acidification with dilute hydrochloric acid. The precipitate was filtered with suction, washed well with cold water and dried in air. A light tan colored product weighing 52 g. (92% of the theoretical yield) and melting at 157-160° was obtained. The crude acid was purified by recrystallization from hot water with the use of decolorizing charcoal. In this manner, colorless needles melting at 165° were obtained. Melting point reported in the literature was 167° (130).

3,4,5-Trimethoxybenzamide

Finely powdered phosphorus pentachloride, weighing 29.3 g. (.141 mole), was placed in a 250 cc. beaker containing 30 g. (.141 mole) of pure trimethylgallic acid. The mixture was quickly stirred as well as conditions permitted. After a few seconds, vigorous reaction took place causing liquefaction and liberation of hydrogen chloride. The reaction mixture was placed on a steam bath for twenty minutes during which time the product assumed colors varying from amber to violet. This liquefied product was then slowly poured with stirring into a 400 cc. beaker containing 100 to 125 cc. of concentrated ammonium hydroxide with pieces of ice floating in it. Vigorous sputtering occurred with the formation of a white to amber colored precipitate. After the addition of the last portion of the acid chloride, the product was allowed to stand in the refrigerator overnight. The precipitate and the crystals were filtered with suction, washed with cold water and air dried. The yield of the slightly amber colored product, melting at 176-177°, was 25.9 g. (87.2% of the theoretical). Melting points reported in the literature is 176°. The colored product can be purified by decolorization with charcoal and recrystallized from water to yield colorless crystals; the melting point does not change.

The method pursued was an elaboration of the technique used by Hurd and Winberg (124). Their method was followed verbatim for about fifteen runs and the best yield obtained was 65%. Instead of "adding an excess of concentrated ammonium

hydroxide to the residue," the procedure was reversed by adding the acid chloride to the excess concentrated ammonium hydroxide as described above.

3,4,5-Trimethoxybenzonitrile

3,4,5-Trimethoxybenzamide, weighing 44.3 g. (.21 mole), was introduced into a three-liter round-bottomed flask equipped with an efficient reflux condenser and 1.5 liters of commercial benzene added. The material was partially dissolved by means of slight heating. Then 43.6 g. (.21 mole) of phosphorus pentachloride was finely powdered in a mortar under a hood and slowly introduced into the reaction flask. The mixture was gently refluxed intermittently for a period of fifteen hours. At the close of this period, benzene was removed by distillation under reduced pressure until a dark semi-solid residue was obtained.

The residue was extracted with five 150-200 cc. portions of isopropyl ether using sufficient heat to obtain a saturated solution for each extraction. After storing the ethereal extracts overnight in the refrigerator, shiny and yellowish needle-like crystals were obtained which after air-drying possessed a strong odor of phosphorus pentachloride or hydrogen chloride. These crystals were then stirred into cold distilled water, filtered with suction, washed four or five times with small portions of cold distilled water and the product dried in a desiccator over calcium chloride and later transferred to a desiccator containing phosphorus pentoxide. A yield of 39 g.

(97.5% of the theoretical) of the tan colored material melting at 90-92° was obtained. Further purification by repeatedly recrystallizing from dry isopropyl ether resulted in colorless crystals melting sharply at 91.1-91.2° (Anschutz thermometer).

This method is essentially the same as that described briefly by Hurd and Winberg (124) in whose directions experimental details were lacking.

3,4,5-Trimethoxy- and 3,5-Dimethoxy-4-hydroxypropiophenone

Preliminary Notes

Magnesium turnings used in the Grignard reaction were prepared by drying the bright commercial turnings in a shallow beaker in a desiccator over phosphorus pentoxide for four to six months prior to its use.

Ether used in the Grignard reaction was prepared by allowing commercial diethyl ether (Baker's) to stand in amber colored one gallon bottle containing one pound of anhydrous calcium chloride (8 mesh) filled to its capacity and allowed to dehydrate for six months.

Toluene used in conjunction with ether in the Grignard reaction was prepared by drying commercial toluene with anhydrous calcium chloride overnight and storing it for six months in an amber colored one gallon bottle containing sodium wire.

The apparatus used for the Grignard reaction was assembled and prepared in the following manner:

A one liter three-necked flask was equipped with an electrically driven, efficient, snugly fitting glass stirrer lubri-

cated with heavy liquid petrolatum; a reflux condenser with a drying tube containing alternating layers of anhydrous calcium chloride and soda lime; and a 125 cc. dropping funnel stoppered with another drying tube similarly fashioned. Paraffined cork stoppers were used for all connections, except for the connection holding the stirrer which was a rubber stopper cleaned with benzene. This apparatus was heated with a low flame simultaneously sweeping dry air through it for at least five hours and allowing it to stand overnight before use.

The procedure followed was precisely the same as that described by Haller and Schaffer (123) who used isobutyl magnesium bromide as their Grignard reagent.

The Grignard Reaction

To the Grignard reagent, prepared from 27.2 g. (.25 mole) of ethyl bromide in 265 cc. of dry ether and 6.08 g. (.25 mole) magnesium turnings, 19.3 g. (.1 mole) of 3,4,5-trimethoxybenzonitrile dissolved in 200 cc. of dry toluene was slowly added dropwise over a period of thirty minutes. The reaction mixture was then heated and refluxed by means of an oil bath at 40-55° for two hours. After this period the ether was removed by reduced pressure distillation from the top of the reflux condenser and dry toluene added to maintain the original volume. This replacement was necessary because according to Haller and Schaffer, when the reaction was carried out in ether only, in which the nitrile is slightly soluble, about two-thirds of the starting material was recovered unchanged.

After all of the ether had been replaced by toluene the mixture was refluxed for three hours at the refluxing temperature of toluene. The reaction mixture was allowed to cool slightly and then poured with stirring into a beaker containing 30 cc. of concentrated hydrochloric acid and ice. The aqueous layer which contains the hydrochloride of the ketimide was washed twice with ether (E) to remove traces of unreacted nitrile, placed in an open beaker and heated on the steam bath until all the dissolved ether was removed. The aqueous layer (C) was then boiled for two hours under reflux and cooled. The dark brown colored oil that separated as a result of hydrolysis was removed by extraction with fifteen 75 cc. portions of ether. The ethereal extract was then washed five times with 100 cc. portions of 5% sodium hydroxide (A) twice with distilled water and the ethereal solution (B) containing the 3,4,5-trimethoxypropiophenone was dried with anhydrous sodium sulfate overnight.

When the crude ethereal extract was washed with the first 100 cc. portion of 5% sodium hydroxide, the alkaline aqueous layer became dark showing slight oxidation due to the presence of free phenolic hydroxyl group which subsequently formed the sodium phenolate. This alkali soluble fraction (A) was acidified with dilute sulfuric acid and the separated product completely removed by extraction with ether. The ethereal solution (D) which now contained the 3,5-dimethoxy-4-hydroxypropiophenone was washed with three 100 cc. portions of water and dried with anhydrous sodium sulfate overnight.

On removal of ether from the ethereal solution (D) under reduced pressure, buff colored velvety crystals were obtained which melted at 96-100°. Yield of this crude product was 3 g. or 14.2% of the theoretical assuming complete reduction to 3,5-dimethoxy-4-hydroxypropiophenone. Dilute alcoholic solution of this product gave a green coloration with ferric chloride test solution thus indicating a free phenolic hydroxy group. When purified by dissolving in absolute alcohol and forcing out with ether, white crystals resulted which melted at 109.0° (Anschutz thermometer). Value reported in the literature was 109-110° (190).

The amber colored crystalline mass remaining after the removal of ether from the ethereal solution (B) was distilled under reduced pressure. On cooling, 12.5 g. (55.8% of the theoretical) of colorless crystals, melting at 52°, were obtained. Bogert and Isham (116) reported 53.5° for this product which they obtained in glistening colorless crystals by recrystallizing the brownish crystalline mass from ligroin. Asahina (121) reported 53°. Mauthner (120) observed 51-52°.

The organic layer (E) was evaporated to dryness on a steam bath and several extractions were made with isopropyl ether. The isopropyl ether was allowed to evaporate spontaneously until crystallization was induced, then filtered by using suction and recrystallized again from isopropyl ether. These crystals when dried melted sharply at 92° and hence were identified as unreacted 3,4,5-trimethoxybenzonitrile.

3,4-Dimethoxypropiophenone

Catechol Dipropionate

In a capacious beaker, 55 g. (.5 mole) of catechol and 92.5 g. (1 mole) of propionyl chloride were placed. Almost immediately liberation of hydrogen chloride and effervescence occurred. The reacting substances were placed on a steam bath for thirty minutes at which time the reaction subsided, resulting in a dark brown colored oil. This oil was taken up in 200 cc. of ether and the ethereal solution was washed three times with 25 cc. portions of 10% sodium hydroxide solution to remove the unreacted portion of catechol. The washed ethereal solution was placed in a large porcelain evaporating dish and the ether removed using steam bath, and the residual oleaginous product was distilled under reduced pressure. In this manner, 99.5 g. or 89.6% of the theoretical yield of the clear, colorless product distilling at 196-97°/60 mm. was obtained. Constants described in the literature by Rosenmund and Lohfert (127) for catechol dipropionate are 281°/760 mm. and 153-57°/14 mm.

Propionyl Catechol

This ketone was prepared according to the method of Miller, Hartung, Rock and Crossley (189) with slight modifications.

In a one liter, three-necked flask, equipped with a stirrer, a dropping funnel, and a reflux condenser, 65 g. of anhydrous aluminum chloride and 400 cc. of carbon disulfide were

placed. To the agitated suspension was added a solution of 11 g. (.1 mole) of catechol in 22.2 g. (.1 mole) of catechol dipropionate; the addition which was governed by the rate of refluxing took about ten minutes. Stirring was continued at room temperature under a hood until the vigorous reaction subsided. The reaction flask was placed on a steam bath for thirty minutes and gently refluxed. The reflux condenser was then removed and heating continued until carbon disulfide was removed and left a slight yellow colored unctuous mass. Dilute hydrochloric acid (1:1), 300 cc., was cautiously added over a period of fifteen minutes and agitated until complete solution resulted. When sufficiently cooled, the supernatant oil was extracted with four 100 cc. portions of benzene. The benzene from the combined extracts was partially removed under pressure, and the residual benzene solution was placed in a beaker and stored in the refrigerator overnight. In the morning, colorless crystals were filtered off and placed in a vacuum desiccator until dry. A product melting at 165° was obtained and the yield was 11 g. or 33.4% of the theoretical.

3,4-Dimethoxypropiophenone

A solution of sodium hydroxide was prepared by dissolving 15 g. (.375 mole) in 100 cc. of water and cooled to room temperature and placed in a three-necked flask equipped with a reflux condenser, a mechanical stirrer, and a dropping funnel. Propionyl catechol, 9 g. (.054 mole), was added; darkening of color occurred due to oxidation. Dimethyl sulfate, 15 g. (.12 mole), was added with constant agitation over a period of thir-

ty minutes. The reaction flask became warm. After the addition of all of the dimethyl sulfate, an additional portion of 15 g. of dimethyl sulfate was added at the same rate as the first portion. At the end of this addition, 10 cc. of 10% sodium hydroxide was added and refluxing maintained for three hours with the aid of gentle heat.

The reaction mixture was cooled and extracted several times with 30-50 cc. portions of benzene. The combined benzene extracts were placed overnight over anhydrous sodium sulfate; the solvent was removed under reduced pressure until a thick oil was obtained. The thick oil was placed in a vacuum desiccator containing paraffin shavings until crystallization occurred. The dark colored crystalline mass thus obtained was purified by crystallization from petroleum ether and a product melting at 62-63° was obtained and the yield was 4.3 g. or 43% of the theoretical. The yield for the compound could be greatly improved.

3,5-Dimethoxypropiophenone

In a one liter three-necked flask equipped with an efficient stirrer, a reflux condenser, and a thermometer, was placed 375 g. of 20% sulfuric acid oleum. Heating and stirring were commenced until a temperature of 175-200° was reached. One mole (122 g.) of benzoic acid was carefully introduced over a period of time. After the final addition, the mixture was heated to 240-50° and kept there for a period of six to eight hours.

The sulfonation mixture was cooled and was slowly poured, with constant stirring, into a large beaker containing 500-750 g. of ice. The sulfonic acid passed into solution. Some sulfone was formed during the reaction but this was removed by filtration. A suspension of barium carbonate, prepared by mixing 250 g. of barium carbonate and 500 cc. of water, was cautiously introduced into the acid mixture. The addition was continued until the solution was no longer acid to litmus. Barium sulfate which had precipitated out was removed by filtration. The filtrate containing the barium salt of 3,5-dihydroxybenzoic acid was concentrated to dryness on a steam bath until the salt crystallized out.

The barium salt was fused with equal weights of sodium and potassium hydroxide at 280-310° for one hour. After cooling, the reaction mixture was carefully dissolved in water, cooled and acidified with concentrated hydrochloric acid. This mixture was placed in the ice box until crystallization occurred. The product was filtered and purified by decolorization with charcoal and recrystallized from hot water. The purified compound melted at 212-215° and weighed 45 g. or 37.5% of the theoretical weight. Melting point reported in the literature (129) was 230°; mixed melting point caused no depression.

3,5-Dimethoxybenzoic acid

One-half mole of sodium hydroxide (20 g.) was dissolved in 160 cc. of water, placed in a 500 cc. three-necked flask equipped with a condenser, a mechanical stirrer and a dropping

funnel, and cooled to about 15°. With stirring, 11.4 g. (.074 mole) of 3,5-dihydroxy benzoic acid was slowly added over a period of fifteen minutes. This constant agitation was kept up throughout the course of the experiment.

Dimethyl sulfate (26.8 g., .217 mole) was slowly added dropwise. Temperature rise was noted. A second portion of 20 cc. of dimethyl sulfate was added similarly and the reaction mixture refluxed gently for two hours. In order to saponify the methyl ester, the mixture was made distinctly alkaline to litmus and refluxing continued for two additional hours.

The product was cooled and acidified with dilute hydrochloric acid. The precipitate was filtered by suction, washed with cold water and dried in air; 11.4 g. (84.5% of the theoretical) of the tan colored product sintering at 171° and melting at 177° was obtained. This product was not purified any further.

This method of synthesis is an adaptation of Mauthner's method of methylation (130).

3,5-Dimethoxybenzamide

Phosphorus pentachloride, weighing 11.4 g. (.055 mole), was finely powdered in a mortar under a hood and added into a 150 cc. beaker containing 10 g. (.055 mole) of finely powdered 3,5-dimethoxybenzoic acid. The mixture was well agitated with a stirring rod until fumes of hydrogen chloride were given off and effervescense resulted, and then placed on a steam bath for fifteen minutes.

The amber colored liquefied product was cautiously poured with constant stirring into a 400 cc. beaker containing 100 cc. of concentrated ammonium hydroxide with pieces of ice floating in it. A slightly yellow colored precipitate immediately formed; the product was set aside in the refrigerator overnight. The precipitate and the fine needle-like crystals were filtered with suction, washed with cold water, decolorized with charcoal and recrystallized from water. In this manner, 6.6 g. (66.4% of the theoretical) of the colorless crystals of the amide melting at 145° were obtained. Suter and Weston (129) reported 146°. Mauthner (133) has obtained 148-149°.

3,5-Dimethoxypropiophenone

The method pursued for this synthesis was essentially the same as the general one reported by Suter and Weston (129). Grignard reagent was prepared from 18.4 g. (.766 mole) of dry magnesium turnings, 83.3 g. (.766 mole) of purified ethyl bromide (Baker's) and 200 cc. of dry ether in the apparatus previously described. (See "Preliminary Notes" on page 53.) 3,5-Dimethoxybenzamide (23.5 g., .1296 mole), previously dried for one week over phosphorus pentoxide in a vacuum desiccator, was introduced into the reaction flask by means of a 125 cc. Erlenmeyer flask connected to the reaction flask with a rubber sleeve and fed in as rapidly as the refluxing of the ether would permit. A further 300 cc. portion of dry ether was added and the reaction mixture was refluxed and stirred intermittently for seventy-two hours. A slightly greenish buff color-

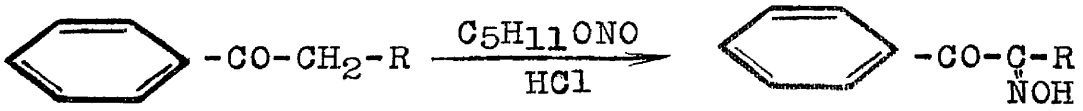
ed precipitate resulted in the reaction flask.

The product was slowly poured into a liter beaker containing a mixture of ice and 75 cc. of concentrated sulfuric acid. The aqueous layer was separated, placed on a steam bath until all of the dissolved ether was removed and then refluxed for three hours. The dark oily layer was removed by extraction with ten 75 cc. portions of ether. The combined ethereal extracts were then washed twice with water and dried with anhydrous sodium sulfate overnight.

On removal of the ether under reduced pressure and distilling the residue under similar condition, there was obtained 21 g. (84% of the theoretical) of an almost colorless oil which solidified into a crystalline mass. The crystals were washed with ice water and dried; the colorless crystals thus obtained melted at 33.5° (Anschutz thermometer). Suter and Weston reported 32.5°. Mauthner (128) reported 34-35°.

II. Nitrosation of Ketones

Claisen and Manasse (134) first described in 1889 a nitrosation reaction applicable to ketones producing oximinoketones according to the following equation:



By using methyl nitrite as the nitrosation agent, Slater (135) was able to prepare these isonitrosoketones in pure and in good yields. Hartung and his associates further showed this

nitrosation reaction is a general one and can be applied to aromatic ketones containing various positive or negative substituents on the nucleus.

In this investigation, this general nitrosation reaction was applied to the alkoxylated propiophenones using n-butyl nitrite as the nitrosating agent following the procedure exactly as outlined by Hartung and Munch (136).

General Nitrosation Procedure

A liter, three-necked, round-bottomed flask is fitted with an electrically driven, snugly-fitting, efficient glass stirrer lubricated with heavy liquid petrolatum, a reflux condenser and a tapering glass delivery tube for the hydrogen chloride. The dry hydrogen chloride generator consisted of a liter round-bottomed flask, containing the concentrated hydrochloric acid, stoppered with an outlet tube and a 125 cc. separatory funnel containing the concentrated sulfuric acid. The hydrogen chloride outlet tube passed through a series of three 125 cc. Erlenmeyer flasks, the center Erlenmeyer flask containing sufficient concentrated sulfuric acid to allow the delivery tube to dip slightly below the surface of the acid, and the remaining two Erlenmeyer flasks being empty and acting as safety flasks.

The appropriate ketone (varying in weight from .03 to .28 mole) was placed in the reaction flask and 350 to 400 cc. of commercial ether added and stirred until solution was effected. Hydrogen chloride gas was generated and passed through the

stirred solution at the rate of two to three bubbles per second, stirring and the addition of the gas being continued throughout the reaction. After the ether solution was saturated with hydrogen chloride (10 to 15 minutes) recently prepared or freshly distilled n-butyl nitrite, b.p. 75-81°, was added through the reflux condenser in 2 to 3 cc. portions until the amount of n-butyl nitrite equivalent to the amount of the ketone taken was added.

After the addition of the first portion the reaction mixture slowly became orange-brown and after several minutes a lighter color, after which a second portion was added. These color changes occurred after the addition of each subsequent portion of the nitrite. After the addition of the last several portions, the orange-brown color remained. During the reaction the mixture gradually warmed up and gentle refluxing occurred. After all of the n-butyl nitrite had been added, stirring and the addition of the hydrogen chloride were continued for another fifteen minutes and the mixture was then allowed to stand overnight at room temperature during which time it became quite dark.

The ethereal solution was slowly stirred into a dilute sodium hydroxide solution containing pieces of ice and the ethereal layer was repeatedly extracted with the cold alkali until no more product was obtained. The alkaline extracts were slowly stirred into concentrated hydrochloric acid containing sufficient ice to keep the reacting mixture cool. In this manner white crystals of appropriate isonitrosopropiophe-

nones were obtained in varying amounts of yields of 36 to 82%. These crystals were further purified by the use of suitable solvents.

n-Butyl Nitrite

n-Butyl nitrite used in these experiments was prepared by the method of Noyes (137). In a three liter, three-necked, round-bottomed flask, fitted with a mechanical stirrer, a separatory funnel extending to the bottom of the flask and a thermometer, were placed 380 g. (5.5 mole) of chemically pure sodium nitrite and 1500 cc. of water. The flask was surrounded by an ice-salt mixture, and the solution stirred until the temperature reached 0°. A mixture of 100 cc. of water, 136 cc. (250 g., 2.5 mole) of concentrated sulfuric acid and 457 cc. (370 g., 5 mole) of commercial n-butyl alcohol previously cooled to 0° was introduced by means of the separatory funnel beneath the surface of the nitrite solution with stirring.

The alcoholic solution was added slowly enough so that practically no gas was evolved; the temperature was kept at 0° ± 1. The resulting mixture was allowed to stand in an ice-salt bath until it separated into layers, and the liquid layers were decanted from the sodium sulfate into a separatory funnel. The lower aqueous layer was removed and the butyl nitrite layer washed twice with 50 cc. portions of a solution containing 2 g. of sodium bicarbonate and 25 g. of sodium chloride in 100 cc. of water. After drying over 20 g. of anhydrous sodium sulfate, the yield of practically pure butyl nitrite amounting to 440 g. (85%)

was obtained. This product was distilled under reduced pressure, and in this manner 400 g. of pure n-butyl nitrite was obtained. n-Butyl nitrite boils at 75° at atmospheric pressure.

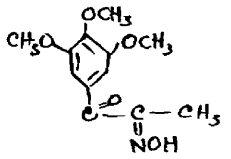
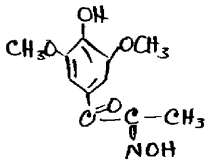
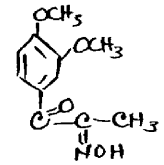
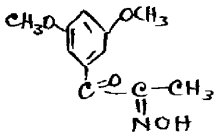
Qualitative Test for Oximation

A few tenths of a gram of the products obtained from the general nitrosation reaction was dissolved in dilute alcohol; a few drops of a saturated solution of hydroxylamine sulfate was added and the mixture carefully made alkaline with a few drops of dilute solution of sodium hydroxide until alkaline to litmus. It was then placed in a water bath for ten minutes and a few drops of ammoniacal nickel sulfate solution added. Immediate brilliant red colored precipitates indicated the presence of the appropriate glyoximes and hence the formation of the appropriate oximinoketones from the nitrosation reactions.

In this prescribed manner, the general nitrosation reaction was applied to 3,4,5-trimethoxypropiophenone, 3,5-dimethoxy-4-hydroxypropiophenone, 3,4-dimethoxypropiophenone and 3,5-dimethoxypropiophenone. The conditions, results and some physical data of these reactions are summarized in Table IV.

TABLE IV

NITROSATION OF KETONES

Product Obtained	Mole Nitrosated	Purification solvent	M.p.	Yield	Ammoniacal nickel to glyoxime	Nitrogen	
						Calc.	Found
	.05	Toluene	145-146°	79.1%	Blood red ppt.		
	.034	Benzene	160-164	36.6	Blood red ppt.	5.85%	5.80% 5.82
	.282	95% Ethanol	163	82.2	Blood red ppt.	6.28	6.20 6.23
	.103	Benzene or 20% Ethanol	107-108	73.9	Blood red ppt.		

III. CATALYTIC REDUCTION TO AMINO ALCOHOLS

Up to the time of Rosenmund and Pfankuch (138) catalytic reduction of oximes and nitriles gave a mixture of primary and secondary amines with the latter often predominating (139,140, 141). In each of these instances the nature of the solvent was neutral being either aqueous or non-aqueous.

Rosenmund and Pfankuch were the first to prevent the formation of the secondary amine by using the acetate of the oxime and an acetic acid solution of the nitrile. Two years later Carothers and Jones (142), using platinum catalyst in acetic anhydride solvent, reduced several nitriles to the corresponding primary amines, isolating them as their acetyl derivatives.

In the extension of this problem, Hartung (143,144) was able to reduce catalytically oximes to the primary amines uncontaminated with the secondary amines by the use of three equivalents of hydrogen chloride in absolute alcohol in the reduction mixture and using palladinized charcoal as a catalyst. Results of the study under such conditions indicated the following:

1- All isonitrosoketones in which the aromatic portion is a hydrocarbon radical; that is, phenyl, m- and p-tolyl, napthyl, the reduction goes smoothly and completely to the corresponding amino alcohol.

2- In those cases where the aromatic portion of

the molecule is substituted by a phenolic hydroxyl or its methyl ether, the reduction stops at the amino ketone stage and the resulting compound may be isolated and purified as its salts, and then reduced to the corresponding amino alcohol in aqueous solution with a new catalyst.

3- The influence of hydrogen chloride operates in three distinct ways. First, it is responsible for the hydrogenation of the oximino portion; second, it has a marked effect on the rate of hydrogenation; and third, it prevents the formation of contaminating secondary and tertiary bases.

This method of catalytic reduction has been successfully carried out in these Laboratories by Foster (44) in the synthesis of p-aminopropadrine, by Zenitz (59) in the synthesis of halogen ring substituted propadrines, by Barry (145) in the synthesis of α-aminoacids, by Dittrich (146) in the synthesis of α-amino-β-hydroxyacids, and by Gakenheimer (147) in the synthesis of aminoalcohols of pharmacologic interest.

In this final phase of the investigation, the aralkoxy oximinoketones were catalytically reduced ultimately to the corresponding amino alcohols pursuing the reduction method mentioned above.

All-Glass Hydrogenator

The apparatus used was the one devised by Hartung consisting essentially of a reaction flask, a mechanical agitator, a train of devices to dry the hydrogen gas, an aspirator, and a pair of inverted graduated cylinders containing hydrogen gas under approximately thirty inches of hydrostatic pressure. The apparatus is nearly of all-glass construction.

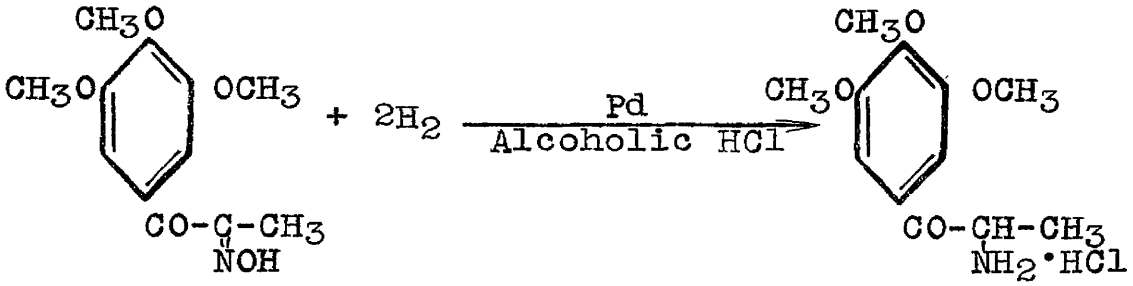
Preparation of Catalyst

In a 125 cc. round-bottomed flask, .3 g. of palladium chloride (10% of the weight of charcoal), 3 g. of Nuchar (Activated Vegetable Carbon, Industrial Chemical Sales, New York City) and 100 cc. of distilled water were placed; this flask was then fitted onto the hydrogenator. The air was removed by evacuating the apparatus, filling it with hydrogen and repeating the process at least four times; this left an atmosphere of practically pure hydrogen. Agitation was allowed to go on until no more hydrogen was taken up. The catalyst thus obtained was filtered off, washed thoroughly with distilled water, finally once with ethyl alcohol and was kept in a vacuum desiccator over concentrated sulfuric acid for at least overnight before use.

Hartung (148) has pointed out that the use of sodium acetate in the preparation of the palladium charcoal produces a catalyst of high activity. This type of catalyst was used in several of the reduction reactions because of somewhat sluggish results obtained from use of the catalyst not prepared through

the intermediation of sodium acetate. Catalyst so prepared was used over and over again and still retained its activity. The method of preparation was essentially the same except for the use of 100 cc. of 1 N sodium acetate in place of the 100 cc. of distilled water.

Reduction of 3,4,5-Trimethoxyisonitrosopropiophenone



Into a 125 cc. reaction flask, 2.53 g. (.01 mole) of the purified 3,4,5-trimethoxyisonitrosopropiophenone and 33 cc. of 2.12 N alcoholic hydrogen chloride (approximately three equivalents of hydrogen chloride) and 17 cc. of commercial absolute alcohol were placed and agitated until complete solution resulted. About 3 g. of the freshly prepared palladinized charcoal catalyst was then introduced and the flask fitted onto the hydrogenating apparatus. The air was removed by evacuating the apparatus, filling it with hydrogen and repeating the process at least four times. No hydrogen was taken up until agitation was begun. Hydrogen uptake was rapid at first and gradually tapered off until no more hydrogen was taken up.

Data were collected and plotted (amount of hydrogen absorbed on the ordinate and time on the abscissa) during the progress of the reduction. The plotted curve reached a maxi-

mum in forty minutes and plateaued off to a constant value when approximately two moles of hydrogen were taken up, indicating that the reduction proceeded to the aminoketone stage and stopped. The behaviour seems to be a general one with methoxy ring substituted isonitrosopropiophenone; and it is in agreement with the observation made by Hartung (144) who noted and concluded that when the aromatic portion is substituted by a phenolic hydroxyl or its methyl ether, the reduction in acid medium stops at the aminoketone stage.

The course of the reduction proceeded in the following manner:

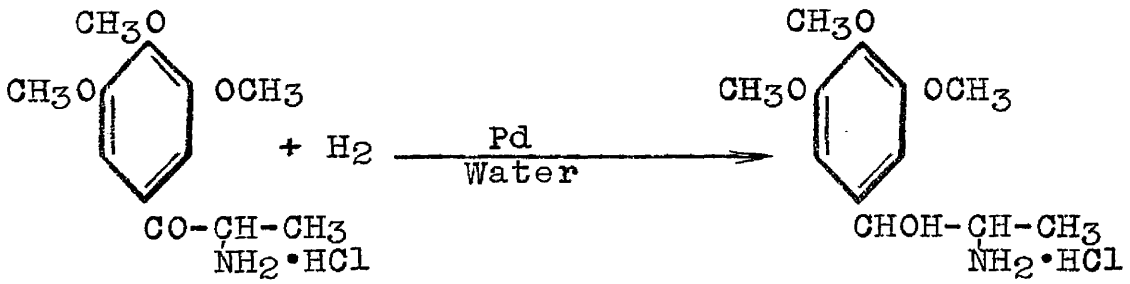
Time in Minutes	Hydrogen Absorbed in cc.*
0	0
8	165
13	240
16	270
18	300
22	345
25	380
27	400
32	430
37	450
44	460
49	465(two equivalents)
52	465
57	465

* All readings of the amount of hydrogen absorbed reported in this dissertation are uncorrected for temperature and pressure.

The reaction mixture was separated from the catalyst by filtration. Filtration was repeated twice more to remove completely fragments of charcoal in the filtrate. During the filtration it was observed that the charcoal catalyst had a whit-

ish appearance. This was due to the low solubility of the aminoketone hydrochloride in the alcohol since more yields were able to be obtained upon elutriation of the charcoal catalyst with 95% alcohol. White crystals separated from the combined alcoholic solution on standing overnight at room temperature. The yield was 1.7 g. (70.8% of the theoretical). The crystals of hydrochloride salt melted with frothing, evolution of gas and decomposition into a dark brown porous substance at 248-49°. (Anschutz thermometer used). Small sample of an aqueous solution of the crystals reduced Fehling's solution on warming. Kjeldahl (Hengar technique): Nitrogen calculated for $C_{12}H_{17}O_4N \cdot HCl$, 5.08%; Nitrogen found, 5.01% and 4.99%.

Reduction of 3,4,5-Trimethoxyphenyl-α-aminopropiophenone



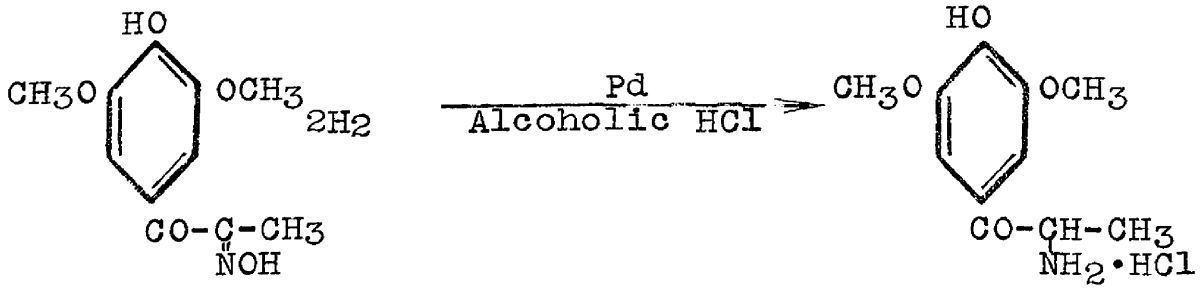
Pure 3,4,5-trimethoxyphenyl-α-aminopropiophenone hydrochloride, 1.0 g. (.0036 mole), was introduced into a 125 cc. reaction flask and 60 cc. of distilled water was added. Using 2 g. of the freshly prepared palladinized charcoal catalyst, the product was hydrogenated in the usual manner. Reduction proceeded smoothly and was completed in thirty-five minutes when one equivalent of hydrogen was taken up as indi-

cated in the data below:

Time in Minutes	Hydrogen Absorbed in cc.	
0	0	
5	30	
10	50	
15	60	
20	75	
25	85	
30	87	
35	90	(one equivalent)
40	90	
45	90	

The aqueous reaction mixture was filtered with suction until clear. It was then placed in a vacuum desiccator over concentrated sulfuric acid and evacuated until an amber colored solid residue, 0.7 g. (70% of the theoretical), was obtained. A small portion of this residue was dissolved in the smallest quantity of absolute alcohol and crystals were forced out by dilution with dry ether. In this manner white crystals of the hydrochloride were obtained which melted at 221.0-221.5° (Anschutz thermometer). The product did not reduce Fehling's solution but formed a violet colored precipitate characteristic of the amino alcohols. Kjeldahl (Hengar technique): Nitrogen calculated for $C_{12}H_{19}O_4N \cdot HCl$, 5.05%; Nitrogen found, 5.01% and 5.07%.

Reduction of 3,5-Dimethoxy-4-hydroxyisonitrosopropiophenone

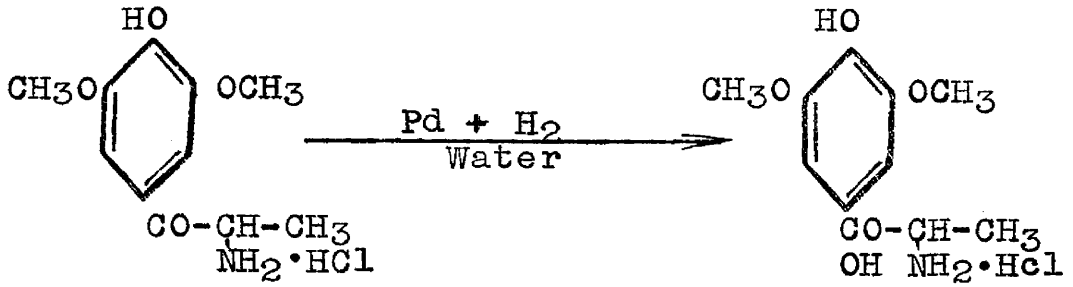


3,5-Dimethoxy-4-hydroxyisonitrosopropiophenone, 1.5 g (.00625 mole), was dissolved in 10 cc. of 2.12 N alcoholic hydrogen chloride and 65 cc. of commercial absolute alcohol, and then 2 g. of palladinized charcoal catalyst prepared by the use of 1 N sodium acetate was introduced. The reduction proceeded rapidly and smoothly until approximately two-thirds of the calculated amount of hydrogen required for complete conversion to amino alcohol was taken up in thirty minutes as shown in the data below:

Time in Minutes	Hydrogen Absorbed in cc.	
0	0	
15	230	
30	290	(two equivalents)
35	290	
50	290	

The reduction product was filtered by suction and a clear lemon yellow colored filtrate resulted. It was placed in a vacuum desiccator over concentrated sulfuric acid until a solid residue remained. A small portion of this tan colored product was dissolved in the least quantity of absolute alcohol and forced out with dry ether. Colorless crystals were obtained which darkened and melted at 209.4° (Anschutz thermometer). Yield of the product was 1.2 g. or 75% of the theoretical. Aqueous solutions of the product with Fehling's solution on warming immediately gave reduction and a green coloration with 10% ferric chloride solution. Kjeldahl (Hengar technique): Nitrogen calculated for $C_{11}H_{16}O_4NCl$, 5.36%. Nitrogen found, 5.34% and 5.47%.

Reduction of 3,5-Dimethoxy-4-hydroxy-α-aminopropiophenone



3,5-Dimethoxy-4-hydroxy-α-aminopropiophenone hydrochloride, 1.0 g. (.00383 mole), dissolved in 30 cc. of distilled water and 2 g. of the activated (via sodium acetate) palladinized charcoal catalyst were introduced into a 125 cc. hydrogenating flask and the reduction allowed to proceed. The reduction was rapid and was complete in fifteen minutes.

Time in Minutes	Hydrogen Absorbed in cc.	
0	0	
5	45	
15	90	(one equivalent)
20	90	
30	90	

The product was filtered until clear and evaporated to dryness in a vacuum desiccator over concentrated sulfuric acid. Six-tenths of a gram (60% of the theoretical) of the tan colored residue was obtained, which melted at 95-98°. Purification by dissolving in absolute alcohol and forcing out with dry ether gave white crystals which could not be obtained pure because of the extreme hygroscopic nature of the compound; the compound liquefied when filtered by suction. This liquefied product became a yellowish solid residue on standing at room temperature overnight. A melting point determination on this

product gave a value of 96° melting with foaming. Kjeldahl (Hengar technique) determination was made on the original tan colored product. Nitrogen calculated for $C_{11}H_{17}O_4N \cdot HCl$, 5.32%. Nitrogen found 7.80%, 7.77% and 7.51%.

The nitrogen analysis appears to indicate that the compound has consistently high percentage of nitrogen. In view of the previous supporting data

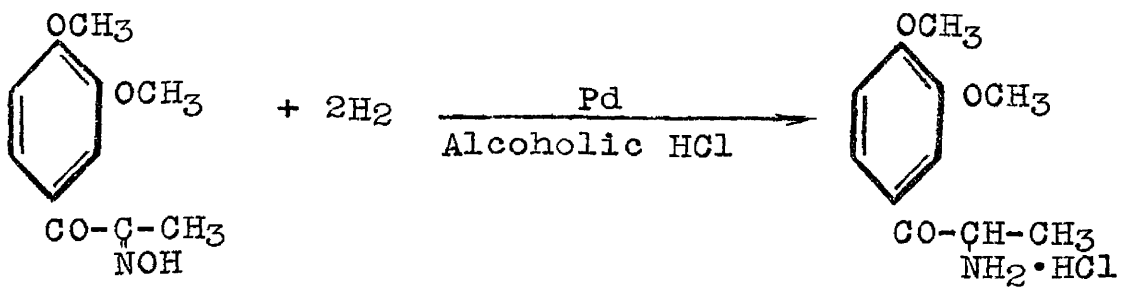
1- that the aminoketone absorbed the theoretical one equivalent of hydrogen,

2- that the aminoalcohol does not reduce Fehling's solution, and

3- that the nitrogen analysis was correct for the aminoketone,

it is the belief that the product experimentally obtained is the correct one. Due to lack of the product, further substantiation could not be obtained.

Reduction of 3,4-Dimethoxyisonitrosopropiophenone



3,4-Dimethoxyisonitrosopropiophenone, 14.5 g. (.065 mole), dissolved in 100 cc. of 2.12 N alcoholic hydrogen chloride and

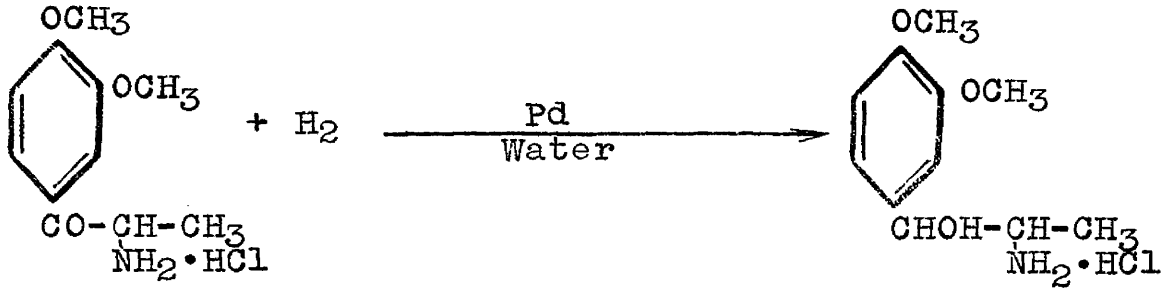
3 g. of the activated palladinized charcoal catalyst were introduced into a 250 cc. reduction flask. Hydrogenation proceeded smoothly until two-thirds of the calculated quantity of hydrogen necessary for complete reduction was taken up when no more absorption was noticed.

Time in Minutes	Hydrogen Absorbed in cc.	
0	0	
5	530	
10	970	
15	1370	
20	1680	
25	1935	
30	2170	
45	2600	
50	2690	
60	2830	
70	2910	
80	2980	
90	3030	
100	3050	
110	3080	
120	3100	
140	3140	
145	3150	
150	3160	
160	3170	
170	3175	
180	3178	
190	3180	(two equivalents)
200	3180	
230	3180	

The reduction mixture was filtered until clear and colorless and concentrated in a vacuum desiccator over concentrated sulfuric acid, one-third its volume of ether was added and placed in the refrigerator overnight. In this manner 10.2 g. (63.4% of the theoretical) of white crystals of 3,4-dimethoxy-α-aminopropiophenone hydrochloride were obtained melting at 214.2° (Anschutz thermometer) with decomposition

and evolution of gas giving a canary yellow melt. Kjeldahl (Hengar technique): Nitrogen calculated for $C_{11}H_{15}O_3N \cdot HCl$, 5.70%; Nitrogen found, 5.65% and 5.68%.

Reduction of 3,4-Dimethoxy-α-aminopropiophenone



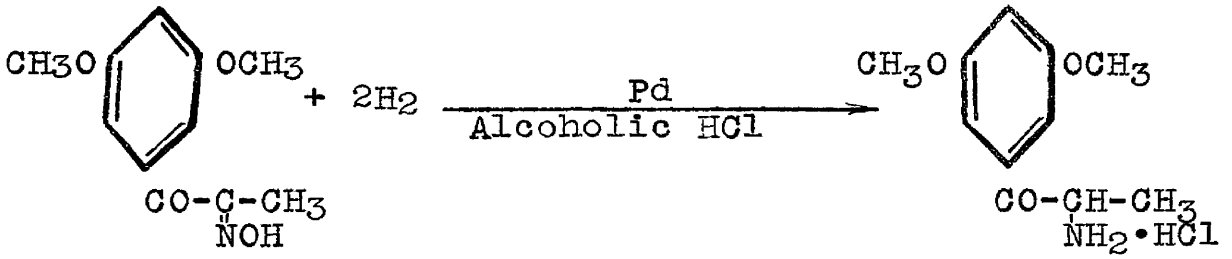
3,4-Dimethoxy-α-aminopropiophenone, 5 g. (.0204 mole), dissolved in 75 cc. of distilled water and 3 g. of activated palladinized charcoal were placed in a 125 cc. reaction flask and hydrogenated. Absorption of hydrogen stopped when approximately one equivalent was taken up as indicated below from the data:

Time in Minutes	Hydrogen Absorbed in cc.	
0	0	
5	140	
10	200	
15	240	
20	270	
25	300	
30	330	
40	370	
50	400	
55	420	
75	450	
90	470	
100	480	
120	500	
135	505	(one equivalent)
140	505	
145	505	

The reduction product was filtered until clear and placed in vacuum desiccator over concentrated sulfuric acid until a

slightly yellow colored solid residue was obtained. The residue was dissolved in the least quantity of absolute alcohol and white crystals were forced out with ether. The crystals when dried weighed 4 g. (80% of the theoretical) and melted sharply at 212.6-213.0° (Anschutz thermometer) with decomposition and evolution of gas to golden yellow melt. Kjeldahl (Hengar technique): Nitrogen calculated for $C_{11}H_{17}O_3N \cdot HCl$, 5.65%; Nitrogen found, 5.54% and 5.67%.

Reduction of 3,5-Dimethoxyisonitrosopropiophenone

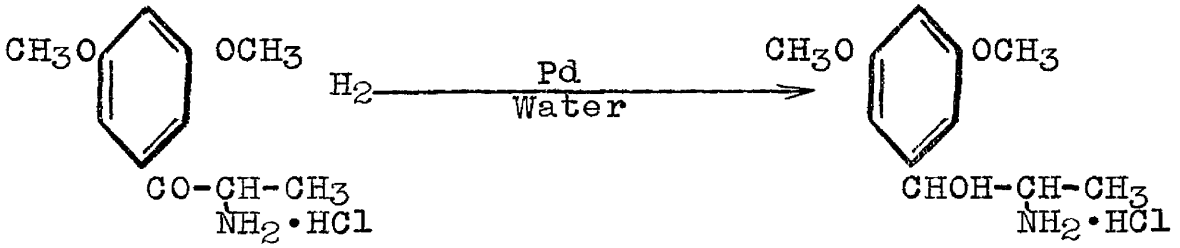


3,5-Dimethoxyisonitrosopropiophenone, 15.5 g. (.0695 mole), dissolved in 100 cc. of 2.12 N alcoholic hydrogen chloride and 50 cc. of commercial absolute alcohol and 3 g. of activated palladinized charcoal catalyst were placed in a 250 cc. reduction flask. Reduction was rapid and completed when two-thirds of the calculated quantity was absorbed thusly:

Time in Minutes		Hydrogen Absorbed in cc.	
0	75	0	2650
5	85	510	2750
15	100	1010	2920
20	115	1310	3010
25	150	1500	3160
35	175	1870	3210
40	185	2070	3230
50	190	2280	3250
60	200	2400	3255 (two eq.)
65	230	2500	3255

The reduction product was filtered and concentrated in a vacuum desiccator and a white crystalline product of the hydrochloride of 3,5-dimethoxy-α-aminopropiophenone was obtained in 12 g. (70.6% of the theoretical) yield. These crystals melted at 204.5° (Anschutz thermometer) with decomposition and evolution of gas to a dark brown melt, and reduced Fehling's solution. Kjeldahl (Hengar technique): Nitrogen calculated for $C_{11}H_{15}O_3N \cdot HCl$, 5.70%; Nitrogen found, 5.66% and 5.64%.

Reduction of 3,5-Dimethoxy-α-aminopropiophenone



3,5-Dimethoxy-α-aminopropiophenone hydrochloride, 12 g. (.048 mole), dissolved in 100 cc. of distilled water and 3 g. of activated palladinized charcoal were placed in 250 cc. reaction flask and hydrogenation carried out to completion. One equivalent of hydrogen was taken up in 240 minutes as shown in the data below:

Time in Minutes	Hydrogen absorbed in cc.
0	0
5	80
10	135
15	185
20	230
25	275
30	315
45	455

(continued)

Time in Minutes	Hydrogen absorbed in cc.
60	610
85	730
120	870
150	1020
180	1130
200	1190
210	1210
220	1220
230	1235
235	1240
240	1245 (one equiv.)
245	1245
250	1245

The reduction product was filtered until clear and placed in a vacuum desiccator over concentrated sulfuric acid until a white residue was obtained. The residue was dissolved in the least quantity of absolute alcohol and white crystals were forced out with approximately 50% mixture of isopropyl and ethyl ethers. In this way 7.8 g. (66% of the theoretical) of crystals melting at 169.5-170.0° (Anschutz thermometer) were obtained. An aqueous solution of a small sample did not reduce Fehling's solution. Kjeldahl (Hengar technique): Nitrogen calculated for $C_{11}H_{17}O_3N \cdot HCl$, 5.65%; Nitrogen found, 5.60% and 5.65%.

This compound has been reported by Bockmuhl, Ehrhart and Stein (84) in a patent granted to I. G. Farbenindustrie in 1935 as having a melting point of 165-167°.

Demethylation of 3,5-Dimethoxyphenylpropanolamine

In a Carius tube, 2.0 g. (.0081 mole) of 3,5-dimethoxyphenylpropanolamine hydrochloride and 10 cc. of concentrated hydrochloric acid were placed, and the tube was sealed and wrapped in towels. It was placed in the steam bath for a period of six to eight hours. After cooling, the tube was carefully opened, and the dark brown mixture emptied into an evaporating dish and the excess hydrochloric acid removed under vacuum over sodium hydroxide pellets. The resulting syrupy residue was finally dried over phosphorus pentoxide under vacuum. In this manner, almost quantitative yield of a tan colored product was obtained. A portion of this product was dissolved in pure n-butyl alcohol and white precipitate forced out with dry diethyl ether. After centrifuging, the solvent was decanted and the white residue dried over phosphorus pentoxide for three days. The product was hygroscopic. The melting point showed unusual behaviour. The product did not liquefy at the melting point, but passed from the crystalline state to the frothing stage without change of color at 195-200°. It decomposed to a carbonaceous mass at a temperature above 250°. An aqueous solution of the product gave a dark violet coloration with ferric chloride test solution and did not reduce Fehling's solution. Kjeldahl (Hengar technique): Nitrogen calculated for $C_9H_{13}O_3N \cdot HCl$, 6.38%; Nitrogen found, 6.15% and 6.25%.

EXPERIMENTAL SUMMARY

For purpose of eventual pharmacological evaluation, five ring-substituted derivatives of propadrine have been synthesized, four of which are being described for the first time. They are

1- 3,4,5-trimethoxypropadrine

2- 3,5-dimethoxypropadrine

3- 3,5-dimethoxy-4-hydroxypropadrine

4- 3,4-dimethoxypropadrine

5- 3,5-dihydroxypropadrine.

3,5-Dimethoxypropadrine hydrochloride is described by Bockmuhl, Ehrhart and Stein (84) as melting at 165-167°. Since the product prepared melted above that previously recorded, it was analyzed to confirm its composition.

The route of reaction was the same in all of the syntheses once the appropriate ketones were synthesized; namely, the nitrosation of the ketones, the catalytic reduction of the oximinoketones, the isolation of the aminoketones, the subsequent catalytic reduction to the corresponding aminoalcohols, and the isolation of the aminoalcohols as the hydrochlorides.

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