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SYNTHESIS OF SELECTED TETRAHYDROISOQUINOLINE ANALOGS
AND THEIR FRAGMENTED DERIVATIVES AS β-ADRENERGIC AGONISTS

DISSERTATION

Presented in Partial Fulfillment of the Requirements for
the Degree Doctor of Philosophy in the Graduate
School of The Ohio State University

By

Peter Fritz Kador, B. A.

****

The Ohio State University
1976

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My Parents, to whom I dedicate this work, for their love, encouragement, understanding, confidence and many sacrifices that have made this possible.
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FIELD OF STUDY

Major Field: Medicinal Chemistry
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INTRODUCTION

Adrenergic drugs are those chemical compounds that produce an effect on the adrenergic nervous system or that part of the peripheral nervous system mediated by the neurotransmitter norepinephrine (1).

Originally epinephrine (2), isolated in the late 1890's from the nerve endings of the adrenal gland[1], was assumed to be the neurotransmitter. Named sympathin and later called adrenaline, the nervous system utilizing epinephrine became known as the sympathetic or adrenergic nervous system. Finally von Euler[2] demonstrated in the late 1950's that norepinephrine (1) is the principal neurotransmitter.

Most of the actions of the adrenergic drugs, which generally resemble responses to the stimulation of adrenergic nerves, may be classified into five broad types: (1) a peripheral excitatory action on certain types of smooth muscle, such as those in blood vessels supplying the skin and mucous membranes, and also on salivary and certain sweat glands; (2) a peripheral inhibitory action on certain other types of smooth muscle, such as those in the wall of
the gut, in the bronchial tree, and in the blood vessels supplying skeletal muscles; (3) a cardiac excitatory action, responsible for an increase in heart rate and force of contraction; (4) metabolic actions, such as an increase in the rate of glycogenolysis in liver and muscles, and liberation of free fatty acids from adipose tissue; and (5) central nervous system excitatory actions, such as respiratory stimulation and with some drugs an increase in wakefulness and a reduction in appetite. These responses, however, are not all shown to the same degree by each adrenergic agonist. 3

Ahlquist 4 demonstrated that the effects of sympathomimetic drugs are elicited through two major types of receptors, $\alpha$ and $\beta$, in the sympathomimetic effector cell. The $\alpha$-receptors mediate contraction in all smooth muscles except those of the non-sphincter regions of the intestinal tract in which they mediate relaxation. The $\beta$-receptors mediate relaxation in all smooth muscles, including those of the intestinal tract and give a positive chronotropic and inotropic response, improved atrioventricular conduction and automaticity (in non-pacemaker cells) of the heart. Some adrenoceptors, particularly those related to the central nervous system, have not yet been successfully classified as either $\alpha$ or $\beta$. This is in part due to technical and interpretive problems associated with central nervous system studies. 5 There may also be some mixing of $\alpha$ and $\beta$ effects as demonstrated by the fact that the intestinal smooth muscle relaxes
to both α- and β-adrenergic stimulants.

Pharmacological evidence for different types of receptors within the general class of β-receptors has accumulated. From studies of the potencies of a number of related catecholamines for producing a variety of "β" responses in both isolated tissues and intact animals, Lands\textsuperscript{6-11} has proposed a $\beta_1$ and $\beta_2$ subclassification for the β-receptor. The $\beta_1$-receptor mediates an increase in the rate and force of contraction of the heart, lipolysis in adipose tissue, and inhibition of smooth muscles in the small intestine. The $\beta_2$-receptor mediates vasodepression, bronchodilation, inhibition of the uterus, glycolysis, muscle glycogenolysis, and a decrease in the tension and duration of maximal twitches of slow-contracting mammalian skeletal muscles. The latter effect is believed to account for the enhancement of physiological muscle tremor observed by $\beta_2$-stimulation\textsuperscript{11}.

This subclassification is open to some criticism due to the experimental methods employed and a discrepancy in the experimental results obtained.\textsuperscript{5} Some of these results may, however, in part be explained by the possibility of having both $\beta_1$- and $\beta_2$-receptors in the same tissue, as observed by Furchgott\textsuperscript{12} in the guinea pig tracheal smooth muscle. The $\beta_1$- and $\beta_2$-adrenoceptors have been termed iso-receptors because they appear to be physiologically identical in mediating biological events, i. e., activating adenyl cyclase, yet differ in sensitivity to certain
agonists and antagonists.\textsuperscript{13} 

The structure activity relationships (SAR) of adrenergic agonists has been widely reviewed.\textsuperscript{14} Structurally adrenergic agonists generally contain a phenethylamine nucleus. Direct acting sympathomimetics, furthermore, generally have structural and stereochemical features closely related to epinephrine (2), i.e., they contain one or more phenolic hydroxyl groups and an alcoholic hydroxyl group $\beta$ to the amino group. Introduction of a bulky N-alkyl substituent increases $\beta$-activity and decreases $\alpha$-activity. In all agonists having one asymmetric carbon $\beta$ to the amino group the R-isomer is more active than the S-isomer.

The physiological responses of $\beta$-adrenergic activation have been extensively related to bronchorelaxation.\textsuperscript{13} Normally the physiological tone of bronchial smooth muscles is balanced by vagal (cholinergic) and sympathomimetic ($\beta$-adrenergic) stimulation. Vagal stimulation results in bronchial smooth muscle constriction, a reflex action which primarily contracts the bronchi in order to protect the aveoli from harmful stimuli. Stimulation of $\alpha$-adrenoceptors also produces bronchial smooth muscle constriction along with vasoconstriction of the bronchial and pulmonary blood vessels and histamine release from mast cells. Stimulation of the $\beta$-adrenoceptors results in the activation of the enzyme adenyl cyclase.\textsuperscript{15,16} In the presence of magnesium ions the adrenergically activated adenyl cyclase facilitates the
intramolecular attack of the 3'-hydroxyl group of ribose on the innermost phosphorus atom of ATP to form cyclic 3',5'-AMP (cAMP). In the lung tissue cAMP then functions as the intracellular mediator of catecholamine action to produce bronchodilation of the bronchial smooth muscles, vasodilation of the pulmonary blood vessels and inhibition of histamine release coupled with a decrease of slow-reacting substance [SRS(A)] from mast cells. Cyclic AMP is, in turn, inactivated to 5'-AMP by phosphodiesterase. These observations are summarized in Figure 1.

Sympathomimetic responses have also been related to bronchial asthma, a disease characterized by variable airway obstruction caused by constriction and excessive secretion and edema resulting from an inflammatory process. Szenti-vanyi in his β-adrenergic theory of bronchial asthma has proposed that asthma should not be regarded as an "immunological disease" but as a unique pattern of bronchial hyperactivity to a broad spectrum of immunological, psychic, infectious, chemical, and physical stimuli. According to this theory bronchoconstriction in the asthmatic individual is cholinergically induced due to a partial blockade of the β-adrenergic system resulting from either a malfunction or deficiency of adenyl cyclase within the smooth muscle cells, glands, or blood vessels of the lungs and tissue mast cells. This adenyl cyclase deficiency may be acquired as a result of infection, genetic inheritance, or by the action of cer-
Factors Affecting the Physiological Tone of Bronchial Smooth Muscles
tain metabolites. Alternatively the sympathomimetic responses may be adequate with the ability of adenyl cyclase to catalyze the production of cAMP becoming limited with time. In this circumstance excessive or prolonged broncho-constrictive stimulation could eventually overcome the counterbalancing bronchorelaxing effects of β-adrenergic stimulation.

This theory has been questioned since asthmatics according to this theory could find little relief with β-adrenergic bronchodilators. A new supplementary theory which states that the disease may be the result of the interaction between decreased circulatory epinephrine and a pathologically altered hyperactive bronchial tree has been proposed. As tentative evidence a decrease in circulatory epinephrine has been noted in some clinical data. This decrease may be secondary to altered uptake or enzyme activity, or from a decreased release of epinephrine from the adrenal medulla.

Therapeutically administration of a β-adrenergic agonist to an asthmatic patient results in an increase in cAMP which in turn results in the relaxation of bronchial smooth muscles and inhibition of chemical mediator increase. The effect of β-adrenergic agonists may be enhanced by the administration of corticosteroids. The level of cAMP may also be increased by the administration of a phosphodiesterase inhibitor. Bronchodilation may also be obtained
by the administration of prostaglandins $E_1$ and $E_2$.\textsuperscript{22}

Ephedrine (3) is the most common oral bronchodilator in use for mild cases of acute asthma and in chronic cases of asthma needing constant medication.\textsuperscript{23} It works both indirectly by releasing catecholamines from sympathomimetic nerve terminals and through direct $\beta$-stimulant activity.\textsuperscript{24} Ephedrine appears to be a weak relatively safe drug with minor central nervous system stimulation, pressor, and cardiac effects. When administered with the phosphodiesterase inhibitor theophylline (4) in order to increase potency, insomnia, central nervous system stimulation, and gastrointestinal upset including vomiting become more important.

\begin{align*}
\text{OH} & \\
\text{CH}_3 & \\
\text{NHCH}_3 & \\
\text{3} & \\
\end{align*}

\begin{align*}
\text{CH}_3 & \\
\text{N} & \\
\text{O} & \\
\text{H} & \\
\text{4} & \\
\end{align*}

Isoproterenol (5) has become a popular bronchodilator because of its rapid and intense activity when administered by inhalation. Its bronchodilating effect, however, is of short duration because isoproterenol is rapidly absorbed from the respiratory tract and metabolized to 3-O-methylisoproterenol (6) by the enzyme catechol-O-methyltransferase (COMT).\textsuperscript{25,26} This metabolite (6) in turn has been shown to be a weak $\beta$-blocker.\textsuperscript{27} Orally the drug is metabolized in the gut and liver by various sulfatase enzymes and by COMT to give the metabolites 7 and 6 respectively.\textsuperscript{28}
Along with its brief duration of action the major disadvantage of isoproterenol is that it activates both \( \beta_1 \)- and \( \beta_2 \)-adrenoceptors producing bronchodilation accompanied by cardiac stimulation and vasodilation. Excessive use of pressurized aerosols containing isoproterenol has been associated with an increase in deaths from asthma possibly due to ventricular fibrillation caused by excessive \( \beta_1 \)-stimulation.\(^{30-32}\)

Therapeutically it would be desirable to synthesize an orally active, direct acting \( \beta_2 \)-adrenergic agonist having a rapid onset and long duration of action. Such an agonist would be a selective bronchodilator with no cardiac or lipolytic activity. In recent years the search for such a new oral agonist has been directed toward chemical modifications of the catecholamine structure by (1) replacement of the 3,4-dihydroxy configuration, (2) replacement of the 3-hydroxyl group, (3) removal of the catechol function, (4)
attachment of a larger substituent on the alkyl nitrogen and alteration of the ethanolamine side chain, and (5) alteration of the phenethyamine moiety.

Orciprenaline (metaproterenol, 8) is an analog of isoproterenol in which the catechol has been replaced by a resorcinol nucleus.\textsuperscript{33} Shifting the 4-hydroxyl group to the 5-position results in a compound no longer metabolized by COMT. Orciprenaline is approximately 10-40 times less active than isoproterenol with no apparent selectivity in adrenergic systems. Orciprenaline has been used in Europe both orally and by aerosol for about 10 years.\textsuperscript{34, 35}

By altering the N-substituent of orciprenaline to a tertiary-butyl group terbutaline (Brincanyl\textsuperscript{9}, 9) has been prepared.\textsuperscript{36} About twice as active as orciprenaline, it is a potent oral bronchodilator agent with prolonged duration of action and relatively large $\beta_2$ vs. $\beta_1$ effects.\textsuperscript{37, 38} Although less known in North America, it has been extensively investigated in Europe for the treatment of bronchospasmic disorders and found to be safe with no evidence of cardiac, hepatic, renal, or hematologic changes.\textsuperscript{39} Its side effects include increased blood glucose levels and a fine tremor of
the fingers.

Increasing the size of the N-substituent of orciprenaline by the introduction of a 2-(4-hydroxyphenyl)propyl substituent produced the third member of the resorcinol family, Th-1165a (fenoterol, Berotec®). This compound appears to be four times as potent as orciprenaline with more selective $\beta_2$- than $\beta_1$-activity. Its $\beta_1$-cardiovascular effects, however, are greater than those of terbutaline.41-44

Replacing the 3-hydroxyl group with the metabolically more stable hydroxymethylene function produced saligenin derivatives which retain some of the electron donating and hydrogen bonding capabilities of the catechol group. Salbutamol (Ventolin®, albuterol, 11) is the most studied of this series of COMT resistant groups.45,46 It is one-fifth as active as isoproterenol in preventing contraction of electrically stimulated isolated guinea pig tracheal muscle and is only a weak $\beta_1$-agonist in guinea pig atrial muscle.47 Intravenous administration to animals indicates that salbutamol is about 20-40 times more active than orciprenaline in preventing bronchial muscle contraction caused by acetylcholine or by a suitable vagal stimulation, histamine,
5-hydroxytryptamine, or bradykinin. It is 2-3 times longer acting than isoproterenol and displays no α-activity.

Clinically salbutamol has been shown to be a potent and selective bronchodilator when administered orally, intravenously, or by inhalation. At doses required for bronchodilator activity little or no cardiac activity is observed. Its activity has been shown to be prolonged upon aerosol administration, an effect attributed to a decreased absorption of the drug. Metabolically, animal studies indicate that salbutamol is excreted unchanged or as the phenolic glucuronide. Skeletal muscle tremors have been observed as a side effect.

Salmefamol (12), a N-2-(4-methoxyphenyl)propyl substituted saligenin, has also been clinically investigated. It also appears to be a selective β₂-agonist with a slightly longer duration of action than salbutamol.

Combining the structural features of salbutamol and terbutaline led to the synthesis of 3-[α-(t-butylamino) methyl]-5-hydroxy-m-xylene-α, α'-diol (13). This compound has been found to possess a β₂-adrenoceptor preference similar to that observed for salbutamol when tested against
histamine induced bronchospasms in both guinea pigs and dogs. In vivo and in vitro comparisons showed to be approximately 100 times less potent than salbutamol and 10 times less than terbutaline with its maximum efficiency as a $\beta_2$-agonist being approximately equivalent to isoproterenol and salbutamol. Its maximum efficiency in the heart, however, was lower than salbutamol and terbutaline.

Replacing the 3'-hydroxyl substituent of isoproterenol with a methanesulfonamide group led to soterenol (14).\textsuperscript{53,54} It is about equipotent with isoproterenol at most $\beta$-receptors but unlike isoproterenol it also possesses a significant $\alpha$-stimulatory action. In anesthetized cats and dogs, soterenol appears to be more active on bronchial muscle than heart muscle.\textsuperscript{55}

In a recent study in which the 3'-hydroxyl substituent of various catecholamines was substituted with sulfonyl and sulfonylalkyl groups the 3-methylsulfonylmethylene-substituted compound, sulfonterol (15) appears to be a promising
new drug. It is about 2 times less potent than isoproterenol in guinea pig tracheal relaxation and 5 times less potent in decreasing pulmonary resistance in cats, with the increase in heart rate being negligible. The most interesting results appear to be in sulfonterol's ability to selectively stimulate the $\beta_2$-adrenoceptor mediating bronchodilation while mediating vasodepression to a lesser extent. Furthermore, no significant skeletal muscle tremors have been observed.

Replacing the 3'-hydroxyl group with a ureido group produced the bronchodilator carbuterol (SK&F 40383-A, 16). In general carbuterol is approximately equivalent to salbutamol in bronchodilation, duration of action, and degree of separation between bronchodilation and cardiovascular stimulant activity. Carbuterol exhibited a somewhat greater separation after oral administration in conscious guinea pigs.

17

18 R = CH(CH$_3$)$_2$

19 R = C(CH$_3$)$_3$
Halogen substituted phenethylamines have been extensively examined. In a series of 2-, 5-, and 6-chlorosubstituted analogs of isoproterenol the 2-chloro analogs 17 and several N-substituted derivatives generally afforded compounds of greater potency than their non-chlorinated counterparts while substitution in the 5- and 6-position decreased β-adrenergic potency as determined in vitro using guinea pig tracheal relaxation and increased rate of right atrial contraction.59 A high degree of bronchodilator versus cardiac specificity or longer duration of action was not obtained.

Clorprenaline (isoprophenamine, 18) has been shown to possess β-adrenergic bronchodilator activity even though it does not possess hydroxyl groups on the phenyl nucleus.60,61 Recently its N-tert-butyl analog 19 (C-78) has been reported to be a selective adrenergic bronchodilator.62 In isolated normal guinea pig tracheal preparations 19 was 3-10 times less potent than clorprenaline in producing relaxation. In isolated atrial preparations 19 showed a biphasic character, producing positive inotropic and chronotropic responses at low concentrations but negative responses at higher concentrations. This suggests that its mechanism of action in the heart may differ from that of isoproterenol. Orally 19 displays a bronchodilating effect more powerful than isoproterenol, salbutamol, or clorprenaline. This possibly may be due to its better absorption from the digestive tract.
The dichloroaniline derivative clenbuterol (NAB 365, 20) has recently been reported to be a selective $\beta_2$-bronchodilator.\textsuperscript{63-65} It appears to have a strong broncholytic response with a long duration of action when administered orally. An oral dose of 10 or 20 $\mu$g was found to be similar in bronchodilating potency to a p. o. dose of 2.5 mg of terbutaline or 20 mg of salbutamol. Clinically clenbuterol has negligible cardiostimulant action and no cardiodepressant activity.\textsuperscript{66} It has been reported to have a blocking effect and only slight intrinsic activity on the $\beta_1$-receptor.\textsuperscript{67}

Attachment of a second epinephrine molecule to the N-alkyl side chain of epinephrine has resulted in the synthesis of hexaprenaline (Ipradol® ST 1512, 21).\textsuperscript{68} It produces broncholytic, vasopressive, and glycolytic effects along with significant cardiac effects.\textsuperscript{69,70} When administered by inhalation hexaprenaline produces bronchodilation comparable to orciprenaline and salbutamol; however, central nervous system stimulation and mild hypoxemia have been
Alteration of the ethanolamine side chain by cyclizing about the α-carbon has led to the synthesis of rimiterol (WG 253, 22). Clinically it is an effective, short-acting bronchodilator with similar β₂-selectivity and potency as salbutamol when administered intravenously to asthmatic patients. As a bronchodilator it has been shown to be 8 times less potent than isoproterenol when administered by aerosol. Its cardiac activity, however, is much less than that of isoproterenol.

Cyclizing the α-carbon back into the catechol ring has led to a series of tetrahydronaphthalene derivatives 23-25. These compounds may be considered conformationally fixed analogs of norepinephrine, epinephrine, and isoproterenol respectively. All three compounds were approximately equipotent to l-isoproterenol in isolated guinea pig tracheal strips and slightly less potent in isolated guinea pig atria. These derivatives are of theoretical importance because all, including the norepinephrine derivative 22, possess essentially only β-adrenergic activity. Furthermore, trans- 24 was 10 times more potent than cis- 24. These results may be explained either by the fact that they are
fixed only in a $\beta$-adrenoceptor favorable conformation or
that the $-\text{CH}_2\text{CH}_2-$ group in the cyclohexane ring may ster-
ically prevent the molecule from access to the $\alpha$-adreno-
ceptor.

\begin{align*}
\text{HOCH}_2\|	ext{NHC(CH}_3\text{)}_3 \quad & \quad \text{26} \\
\text{HOCH}_2\|	ext{NHC(CH}_3\text{)}_2 \quad & \quad \text{27}
\end{align*}

Modifications of the phenethylamine ring system have
been reported. Replacing the benzene ring of salbutamol
with a pyridine ring has produced pyrbuterol (26).78 Prel-
iminary animal studies have demonstrated that pyrbuterol is
a selective $\beta_2$-agonist with a prolonged duration of action
when administered orally.79 Preliminary clinical studies
indicate pyrbuterol to be a well-tolerated, effective long
acting oral bronchodilator that produces a slight change in
pulse and blood pressure.80

Replacing the catechol nucleus with a 8-hydroxyquinol-
line derivative whose potent chelating properties should
mimic those of catecholamines has led to the synthesis of
quinterenol (quinprenaline, 27).81 In vitro it is about
30-50 times less active than isoproterenol on isolated guin-
ea pig trachea and rat uterus and is virtually inactive in
perfused isolated heart of dog, cat, or guinea pig.82 In
vivo orally administered quinterenol is virtually non-selec-
tive, increasing cardiac output and heart rate and reducing
blood pressure in anesthetized and conscious dogs while being nearly as effective as isoproterenol in protecting guinea pigs from bronchospasms induced by histamine aerosol. Its cardiac stimulant properties, however, were different from those of isoproterenol because they were antagonized by chlorpromazine as well as by β-blockers. Furthermore, quinterenol appears to have a slow onset and very long duration of action along with a high affinity for β-adrenoceptors.

Many tetrahydroisoquinoline derivatives have been observed to have sympathomimetic activity. Tetrahydroisoquinoline (28) which may be regarded as a cyclized phenethylamine has been observed in vivo and in vitro to act through an indirect sympathomimetic mechanism. The catecholamine derived tetrahydroisoquinolines 6,7-dihydroxytetrahydroisoquinoline (29) and 4,6,7-trihydroxytetrahydroisoquinoline (30) which may be regarded as a cyclized dopamine derivative and epinephrine respectively have also been shown to possess the properties of false adrenergic neurotransmitters.

A variety of substituted 1,2,3,4-tetrahydroisoquinolines can be obtained from the condensation of catechol-
amines with aldehydes, either at neutral pH\textsuperscript{86} or under the acidic conditions of the typical Pictet-Spengler condensations.\textsuperscript{87} Salsolinol (31), the condensation product of dopamine (32) and acetaldehyde (33), the primary metabolite of ethanol, has been synthesized \textit{in vitro} and is currently proposed to play a part in the physical and behavioral aspects observed after alcohol ingestion.\textsuperscript{88--92} Recently Collins and Bigdeli\textsuperscript{93} have shown that acute ethanol intoxication in rats pretreated with pyrogallol results in the \textit{in vivo} formation of salsolinol in the brain. The S-(-)-isomer of salsolinol has been shown to be more effective than the R-(+)-isomer in inhibition of \textsuperscript{3}H-dopamine accumulation in rat brain slices.\textsuperscript{94}

\[
\text{HO} \quad \text{NH}_2 \quad + \quad \text{CHO} \quad \xrightarrow{\text{CH}_3} \quad \text{HO} \quad \text{NH} \quad \text{CH}_3
\]

\textbf{32} \quad \textbf{33} \quad \textbf{31}

Similarly Holtz and co-workers\textsuperscript{95} found that dopamine which behaves as a pressor agent when administered to a cat was transformed by incubation with monoamine oxidase (MAO) into an agent which lowered the cat's blood pressure. They subsequently identified this depressor agent as tetrahydro-papaveroline (34) and showed that it was formed by a non-enzymatic Pictet-Spengler condensation between dopamine and its monoamine oxidase product, 3,4-dihydroxyphenylacet-aldehyde (35) which is normally oxidized \textit{in vivo} to the
corresponding acid. This formation has been proposed to be enhanced in vitro by ethanol through its primary metabolite, acetaldehyde, which competitively inhibits nicotinamide adenine dinucleotide (NAD)-linked aldehyde dehydrogenase.

\[
\begin{align*}
32 & \xrightarrow{\text{MAO}} \text{HO} & & \text{CHO} & + & 32 & \rightarrow & \text{HO} & & \text{HO} & & \text{NH} & & \text{OH} & & \text{OH} \\
35 & & & & & & & & & & & & & & & 34
\end{align*}
\]

Sourkes has proposed that the therapeutic action of the amino acid L-DOPA in the treatment of Parkinsonian patients may be due to the in vivo formation of tetrahydropapaveroline and related tetrahydroisoquinolines. In support of this hypothesis tetrahydropapaveroline and salsolinol have been identified in the urine of these patients.

Tetrahydropapaveroline, a demethylated and hydrogenated derivative of the spasmolytic papaverine (36), was first synthesized by Pyman in 1909 and reported to show hypotensive activity by Laidlow in 1910. It has been shown to possess β-adrenergic activity similar to that of isoproterenol, mediating cardiac stimulation in rabbits, bronchodilation and inhibition of the uterus in guinea pigs, vasodepression in cats, and lipolysis in rats. These effects could be prevented with the β-blocker pronethalol.

Furthermore, in lipolysis tetrahydropapaveroline and norepinephrine have been shown to act through the same mechanism.
With adenylate cyclases of the rat erythrocyte tetrahydro-papaveroline has been shown to have weak intrinsic activity with the S-isomer being more active than the R-isomer.\textsuperscript{103}

SAR studies of tetrahydropapaveroline indicate that the 1,2,3,4-tetrahydroisoquinoline ring system and a 1-benzyl substituent are essential for activity.\textsuperscript{104,105} Yamato and co-workers\textsuperscript{106} further found that the 6,7-dihydroxy groups were essential with the hydroxyl groups in the 3',4'-positions of the benzyl ring having a secondary role. Furthermore, the latter hydroxyl groups could be substituted advantageously with the alkoxy groups in the 3',4'-position with retention of activity. Based on these studies the 1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, trimetoquinol (Inolin\textsuperscript{®}, tretquinol, \textsuperscript{37}), was synthesized in the research laboratories of Tanabe Seiyaku and Co.\textsuperscript{106,107}

Trimetoquinol has been observed to be the most potent bronchodilator and one of the most potent agents of lipolysis synthesized to date. In guinea pigs its bronchodilating activity \textit{in vitro} and \textit{in vivo} were about 10 and 5 times
stronger respectively than isoproterenol. On the cardiovascular systems of dogs and rats trimetoquinol was 5 times less potent than isoproterenol in producing hypotensive, positive inotropic and chronotropic effects as well as a peripheral vasodilating effect. In conscious guinea pigs it protected against bronchospasms induced by histamine or methacholine aerosol. In vitro lipolysis studies of rat adipose tissue showed trimetoquinol to be 5 times more potent than norepinephrine.

Farmer and co-workers have compared the β-adrenoceptor stimulant properties of trimetoquinol with those of isoproterenol, orciprenaline, salbutamol, and soterenol. In guinea pig tracheal preparations the dose ratios for 50% inhibition were isoproterenol 1, trimetoquinol 2, soterenol 6, and orciprenaline 144. In dose response curves trimetoquinol appeared to be only a partial β-adrenergic agonist producing a plateau effect in the concentration of trimetoquinol producing relaxation at the 75% level of maximum relaxation. Further increases in the concentration of trimetoquinol finally produced 100% relaxation. On isolated atrial preparations trimetoquinol and salbutamol were only partial agonists with respect to both force and rate. Salbutamol, however, displayed a greater agonist activity on rate. The dose ratios with respect of 50% of the maximum rate were isoproterenol 1, soterenol 3.3, orciprenaline 125, and salbutamol 500. Due to the low activity of trimeto-
quinol, a dose ratio value could not be calculated in atria. The dose ratios with respect to force were isoproterenol 1, orciprenalin 63, salbutamol 2500, and for solterenol and trimetoquinol < 10,000. Similar results were obtained by Brittain in rats and guinea pigs. However, a species difference in cardiac responses to trimetoquinol was observed with rat preparations being much more sensitive to trimetoquinol than guinea pig preparations. These initial findings indicated trimetoquinol to be a selective β2-adrenoceptor stimulant.

Trimetoquinol, which contains an asymmetric carbon at the 1-position of the isoquinoline nucleus, has been resolved since it is generally known that on optical isomer of a pharmacological agent is more active than the other but may be antagonized by it. In bronchodilation of isolated guinea pig tracheal muscle the 1-isomer (Inolin, AQL-208) was about twice as active as the racemate with the d-isomer having neither bronchodilation activity nor antagonistic action against the 1-isomer. The isomer was also two times more active than the racemate in protecting against histamine or methacholine-induced dyspnea when administered orally, subcutaneously, or by inhalation to guinea pigs and intravenously to dogs. In lipolysis of rat epididymal fat tissue an isomeric activity ratio difference of 2.9 log units has been determined between the 1- and d-isomers.
With trimetoquinol isomers of known absolute configuration the S-(-)-isomer has been shown to be more active as a lipolytic agent than the corresponding R-(+)-isomer.\textsuperscript{114} In guinea pig bronchodilation the more active S-(-)-isomer displayed an isomer activity difference of 2.0 log units while in guinea pig atria the isomeric difference was nearly equivalent.\textsuperscript{115} The stereoisomers of trimetoquinol were inactive and unable to produce any constriction of aortic strip preparations and were found to be an antagonist of the $\alpha$-adrenoceptor system.

Some discrepancies have been observed between the reported activities of racemic and optically active trimetoquinol in guinea pig atria and trachea. Buckner and Abell\textsuperscript{116} in comparisons with $\perp$-trimetoquinol in guinea pig atria and trachea observed an enantiomeric potency difference of 1.61 and 1.56 log units respectively. Similar results have been reported by Feller, Miller and Venkatraman.\textsuperscript{115} However, contrary to previously reported results\textsuperscript{109,110} Buckner and Abell\textsuperscript{116} observed no selectivity between trachea and atria. They contribute this discrepancy to a considerably longer time-response relationship observed for trimetoquinol compared to isopreterenol and suggest that necessary equilibrium conditions may not have been achieved in the earlier studies.

Clinical studies of the $\perp$-isomer of trimetoquinol indicate that it is an effective bronchodilator when admini-
stered intravenously, subcutaneously, or by inhalation.\textsuperscript{117} It displays a rapid onset of action but a relatively short duration of action. When administered orally trimetoquinol was effective in mild cases but could not be depended upon with moderate to severe asthmatics. Palpitation of the heart was reported to be a common side effect in 27\% of all cases where trimetoquinol was administered by intravenous injections and in 30\% where it was administered subcutaneously. However, no side effects were reported when trimetoquinol was administered orally or by inhalation.

In a double-blind controlled investigation of asthmatic children the $\text{L}$-isomer of trimetoquinol has been shown to be safe and effective in improving wheezing and rales.\textsuperscript{118} Asthmatic conditions were especially subsided in children under 3 years of age. No undesirable side effects were reported.

Distribution studies of $[^3\text{H}]$ trimetoquinol in guinea pigs show that the highest concentration of the drug was found in the kidney with moderate levels in the spleen, heart and lung, and very low levels in the brain.\textsuperscript{119} This distribution pattern was similar to that of $[^3\text{H}]$ isoproterenol; however, in tissues other than liver and kidney the levels of trimetoquinol were higher. After 48 hours 42\% of the drug was excreted in the urine while 49\% was excreted in the feces.
The metabolic pathways of trimetoquinol and isoproterenol have been observed to be similar with the extent of O-methylation and conjugation differing. The major metabolite excreted in the urine of guinea pigs and rabbits was the O-glucuronide while in rats the major metabolite was the O-methylated derivative. O-methyl derivatives conjugated with glucuronic acid along with unchanged trimetoquinol were also observed in the urinary extracts. Species differences were also observed between the capacity of O-methylation and the ratio of the 6- and 7-O-methylated isomers. Furthermore, the O-methylations of l- and d-isomers by liver homogenates of rats and guinea pigs were relatively stereospecific for the l-isomer.

![Chemical Structures](image-url)
The O-methyl metabolites have been pharmacologically investigated and found to be weak β-adrenergic agonists with considerably less activity than trimetoquinol in producing positive chronotropic, hypotensive, and bronchodilator activities. These metabolites, however, displayed β-adrenergic blocking activity on the cardiovascular effect of isoproterenol with the 6-O-methyl metabolite being one-tenth as active as propranalol. The 7-O-methyl metabolite was more potent as a β-blocking agent than the 6-O-methyl metabolite.

Trimetoquinol, although it has been shown to exhibit a weak papaverine-like activity, has been classified as a β-adrenergic agonist because it increases the level of cAMP and competes with propranalol and pronethalol for the β-adrenoceptor. Its effect on cAMP phosphodiesterase has been studied in guinea pig trachea in order to determine if trimetoquinol, like papaverine, increases the level of cAMP through the inhibition of phosphodiesterase. 

At low concentrations (10^{-7} - 10^{-5} \text{ M}) trimetoquinol increased the tissue level of cAMP without affecting the activity of cAMP phosphodiesterase. Papaverine, however, at these concentrations inhibited cAMP phosphodiesterase. At higher concentrations (10^{-5} \text{ M}) some inhibition of cAMP phosphodiesterase activity was observed. From these studies it was concluded that the action of trimetoquinol on tracheal muscle at low concentrations is likely to be the result of activation of adenyl cyclase while at higher con-

centrations the observed inhibition of cAMP phosphodies-
trerase may correlate with weak papaverine-like activity
of trimetoquinol on depolarized smooth muscles. From
studies on rat epididymal fat tissue Piascik, Feller and
Miller have reported that trimetoquinol does not mediate
lipolytic activity through inhibition of cAMP phosphodies-
terase. Neither of the isomers of trimetoquinol were able
to inhibit either low $K_M$ or high $K_M$ phosphodiesterase until
high concentrations ($10^{-4} \text{ M}$) were employed. Furthermore,
at these concentrations ($10^{-4} \text{ M}$) only ca. 20% of the inhi-
bition of papaverine was observed.

Trimetoquinol, which may be considered to be a cyclized
phenethylamine derivative, cannot be directly fitted into
the structural pattern of the phenethanolamines since it
lacks a substituent at C-4 that corresponds to the $\beta$-hy-
droxy l group. This $\beta$-hydroxyl group through its hydrogen
bonding ability is believed to aid in positioning the cat-
ionic nitrogen group in the drug-receptor complex. Iwasawa and Kiyomoto have postulated that trimetoquinol
interacts with the $\beta$-adrenoceptor at three points — the
catechol group, the nitrogen atom, and the aromatic ring of
the 3,4,5-trimethoxybenzyl substituent. Furthermore, this
aromatic ring has been proposed to interact with some struc-
ture in the receptor site and play the role of the $\beta$-
hydroxyl group.
Larsen\textsuperscript{127} has proposed that $\beta$-adrenergic stimulants interact with a nucleophilic center in the $\beta$-adrenoceptor through quinone-methide intermediates. For trimetoquinol the quinone-methide intermediate $41$ could be formed through an internal amine leaving group. This theory, however, fails to explain the rapid onset of the biological response to $\beta$-stimulants and the fascicle termination of their effects by simply washing the tissues. Moreover, Brittain\textsuperscript{109} and Dyke, White and Hartley\textsuperscript{128} have reported that the saligenin analog ($42$) of trimetoquinol which should be capable of forming a quinone-methide intermediate had no useful pharmacological activity.

\begin{center}
\begin{tabular}{c}
\textbf{41} & \textbf{42} \\
\end{tabular}
\end{center}

SAR studies conducted on trimetoquinol indicate that two free hydroxyl groups at the 6- and 7-positions of the tetrahydroisoquinoline nucleus are necessary for optimum activity. Replacement of either of the two hydroxyl groups with hydrogen or masking both hydroxyl groups with O-methyl groups or an ethylene group resulted in a loss of activity.\textsuperscript{105} Interestingly, replacement of the catechol by a saligenin moiety in both $42$ and $43$ resulted in inactive
Studies on the 1-substituent of 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline indicate that a marked loss of activity is observed with variation of the C-1 arylmethyl group or with alteration of the absolute stereochemistry.\textsuperscript{105,109} Substituting with 1-alkyl groups generally resulted in inactive or slightly active bronchodilating compounds, with the 1-isopropyl analog being the most active of the series.\textsuperscript{129} Substitution with an aryl, 2-arylethyl, and 3-arylpropyl group also resulted in loss of activity.\textsuperscript{105} Of the arylmethyl series the 3,4,5-trimethoxybenzyl group was the most active being 40 times more potent than the next reported analog of the series.

Studies on the B ring of the isoquinoline ring indicate a loss of bronchodilating activity when either a double bond is located between C-1 and C-2, or when a methyl group is substituted at positions 2 or 3.\textsuperscript{105} From these studies Iwasawa and Kiyomoto\textsuperscript{105} concluded that a 1,2,3,4-tetrahydroisoquinoline ring system was necessary for optimum bronchodilator activity.
Objectives:

In order to test the hypothesis\(^\text{105}\) that the 1-aryl-methyl substituent of trimetoquinol may substitute for the \(\beta\)-hydroxyl group of phenethanolamine in helping to achieve the proper binding of trimetoquinol within the \(\beta\)-adrenoceptor, the 4-substituted analog \(44\) along with its open-chain nor-epinephrine analog \(45\) has been synthesized. Positionally the arylmethyl group in these compounds corresponds to the \(\beta\)-hydroxyl group of phenethanolamines.

In guinea pig trachea trimetoquinol has been reported to be a partial agonist producing only 75\% of its bronchodilating response by \(\beta\)-adrenergic mechanisms.\(^\text{109,111,122}\) This may perhaps be due to the fact that since the amino group of the tetrahydroisoquinoline ring is held more rigidly in space than the amino group of phenethanolamine, trimetoquinol may not be able to optimally "fit" the receptor. To investigate this possibility the fragmented trimetoquinol derivative \(46\) in which the bond between the C-1 carbon and the aromatic ring has been cleaved in order to produce a totally flexible derivative has been
Although less active than trimetoquinol, this derivative was more selective than trimetoquinol for trachea and lipolysis than for guinea pig atria. Therefore, in order to determine the effect of having a "less flexible" fragmented derivative in which the N-alkyl group is flexible while the aryl methyl group is "tied" to the catechol ring the fragmented derivative 47 has been synthesized. In this compound the bond between the C-4 carbon and the aromatic ring has been cleaved.

Furthermore, in order to study the effect of varying the N-alkyl substituents the less lipophylic primary amine analog 48 and N-methyl analog 49 along with the more lipophylic N-isopropyl analog 50 have been prepared. Also
prepared were the similarly N-substituted 1-(3,4-dihydroxyphenyl)phenethylamines 51-54.

The biological activity of these analogs (51-54) was compared to that of the 1-benzyl analog of trimetoquinol, 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (55).

No reports have been published on the conformational relationships between the two aromatic rings of trimetoquinol. In order to gain some insight into this problem, compound 56 has been synthesized. The attempted synthesis of compounds 57 and 58 is also described.

Compound 56 may be considered a cyclized analog of 49 in which the two aromatic rings are in an anti-relationship. In cis- and trans-2-(3,4-dihydroxyphenyl)-3-(3,4,5-trimeth-
oxyphenyl)pyridine (57 and 58) the two aromatic rings are in varying degrees of a syn-relationship.
RESULTS AND DISCUSSION

This section has been divided into a presentation of the synthetic and biological aspects of this study. The synthesis and attempted synthesis of the trimetoquinol analogs presented under the synthetic section have been divided into three subsections corresponding to their order of presentation in the introduction. The biological section has been similarly subdivided.

A. SYNTHETIC

I. Synthesis of 4-(3,4,5-Trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (44) and 2-(3,4-Dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine hydrochloride (45).

The synthesis of the 4-substituted analog of trimetoquinol (44) is summarized in Scheme 1 on the next page.

Reduction of 3,4-dibenzyloxybenzaldehyde (59) with lithium aluminum hydride in tetrahydrofuran afforded 3,4-dibenzyloxybenzyl alcohol (60) in 97% yield. The alcohol was converted in good yield to the 3,4-dibenzyloxybenzyl chloride (61) with thionyl chloride and sodium acetate in benzene according to the method of Cava and Noguchi.132
Scheme 1

BzI0\(\text{CHO}\) \[\xrightarrow{\text{LAL}}\] BzI0\(\text{CH}_2\text{OH}\) \[\xrightarrow{\text{SOCl}_2}\] BzI0\(\text{CH}_2\text{Cl}\) \[\xrightarrow{\text{NaI, NaCN}}\] BzI0\(\text{CH}_2\text{CN}\)

1. BzI0\[\xrightarrow{\text{B}_2\text{H}_6}\] 2. HCl

1. NaH or LDA
2. CH\(_2\)X

1. BzI0\[\xrightarrow{\text{Et}_3\text{N, Cl}_3\text{CCCHO}}\] 2. POCl\(_3\)

H\(_2/\text{Pd-C}\)

1. NaBH\(_4\)
2. HCl

H\(_2/\text{Pd-C}\)
A slightly cleaner product was obtained in 87% yield by refluxing the alcohol 60 with thionyl chloride in ethyl ether followed by purification with activated charcoal. The 3,4-dibenzylxybenzyl chloride was then converted to 3,4-dibenzylxybenzyl nitrile (62) in 79% yield with sodium cyanide and sodium iodide in methyl ethyl ketone according to Carlson and Lindquist. This nitrile in turn was alkylated with either 3,4,5-trimethoxybenzyl chloride (63) or 3,4,5-trimethoxybenzyl bromide (64) to yield the nitrile 65.

The benzyl chloride 63 and benzyl bromide 64 were prepared from 3,4,5-trimethoxybenzaldehyde (69). Reduction of the aldehyde 69 with sodium borohydride in methanol afforded the intermediate 3,4,5-trimethoxybenzyl alcohol (70) which was converted to either the chloride 63 or bromide 64 by reaction with the appropriate hydrogen halide gas under dehydrating conditions according to a modified procedure of Brown and Kornblum.  

\[
\begin{align*}
\text{CHO} & \quad \rightarrow \quad \text{CH}_2\text{OH} \\
\text{CH}_3\text{O} & \text{OCH}_3 \quad \rightarrow \quad \text{CH}_3\text{O} \\
\text{CHO} \quad \text{69} & \quad \rightarrow \quad \text{CH}_2\text{OH} \quad \text{70} & \quad \text{HX} & \quad \text{CH}_2\text{X} \\
\text{CH}_3\text{O} & \text{OCH}_3 & \text{CH}_3\text{O} & \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{63} & \text{X} = \text{Cl} & \text{64} & \text{X} = \text{Br}
\end{align*}
\]

In initial alkylation experiments no difference was observed between the chloride 63 and the bromide 64 in their ability to be alkylated with nitrile 62. Use of the 3,4,5-
trimethoxybenzyl bromide, therefore, was discontinued on account of its shorter shelf life.

Alkylation of 3,4-dibenzoyloxybenzyl nitrile (62) with 3,4,5-trimethoxybenzyl chloride (63) using sodium hydride in dimethylformamide (DMF) according to a modified procedure of Uff and Kershaw\textsuperscript{138} yielded the monoalkylated product, 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)propionitrile (65) along with a small amount of the dialkylated product, 2-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxybenzyl)-3-(3,4,5-trimethoxyphenyl)propionitrile.

Chromatographic separation of the reaction mixture on silica gel yielded 42% of the monoalkylated product 65, 11% of the dialkylated product and 24% of the starting nitrile 62. Monoalkylated 65 displayed an AX\textsubscript{2} nuclear magnetic resonance (NMR) pattern between the methine and methylene protons while the dialkylated product showed a broad singlet for its methylene protons.

Applying the selective ester alkylation of Creege et al.\textsuperscript{139} in which lithium diisopropylamide (LDA) in tetrahydrofuran (THF) and hexamethylphosphoramide (HMPA) is employed to the nitrile 62 gave the monoalkylated product 65 and unreacted nitrile 62. The alkylated product crystallized cleanly in 45% yield from an ethereal solution of the reaction mixture upon slow evaporative concentration of the solution. Chromatography of the resulting residue yielded 21% of the unreacted nitrile 62. Attempts at optimizing
the yields by increasing the reaction time and temperature appeared to be unsuccessful.

Reduction of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)propionitrile (65) with diborane in THF cleanly afforded in 84% yield 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine (66), isolated as the hydrochloride salt. Reduction of nitrile 65 with lithium aluminum hydride according to Brown et al. yielded in 37% crude hydrochloride 66 which was difficult to purify. Attempted catalytic reduction of nitrile 65 with platinum oxide catalyst yielded only starting material.

Alternatively 66 was obtained from nitrile 62 according to Scheme 2.

\[
\begin{align*}
\text{BzI}0 & \quad \text{BzI}0 \\
\text{62} & \quad \text{62} \\
\text{CN} & \quad \text{CN} \\
\end{align*}
\]

\[
\begin{align*}
\text{1. KOH, } H_2O & \quad \text{1. KOH, } H_2O \\
\text{2. } H_3O^+ & \quad \text{2. } H_3O^+ \\
\text{3. } CH_3OH/H^+ & \quad \text{3. } CH_3OH/H^+ \\
\end{align*}
\]

\[
\begin{align*}
\text{BzI}0 & \quad \text{BzI}0 \\
\text{71} & \quad \text{71} \\
\text{CO}_2CH_3 & \quad \text{CO}_2CH_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{1. LDA} & \quad \text{1. LDA} \\
\text{2. 63, HMPA} & \quad \text{2. 63, HMPA} \\
\end{align*}
\]

\[
\begin{align*}
\text{BzI}0 & \quad \text{BzI}0 \\
\text{73} & \quad \text{73} \\
\text{CO}_2H & \quad \text{CO}_2H \\
\end{align*}
\]

\[
\begin{align*}
\text{KOH} & \quad \text{KOH} \\
95\% \text{ EtOH} & \quad 95\% \text{ EtOH} \\
\end{align*}
\]

\[
\begin{align*}
\text{BzI}0 & \quad \text{BzI}0 \\
\text{72} & \quad \text{72} \\
\text{CO}_2CH_3 & \quad \text{CO}_2CH_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\end{align*}
\]
Hydrolysis of 3,4-dibenzyloxybenzyl nitrile (62) according to the procedure of Carlson and Lindquist\textsuperscript{133} yielded 3,4-dibenzyloxyphenylacetic acid in 69% yield. This acid was quantitatively esterified to the methyl ester 71. Alkylation of methyl 3,4-dibenzyloxyphenylacetate (71) according to Creege et al.\textsuperscript{139} yielded the alkylated ester 72 in 88% yield. The ester 72 was then hydrolyzed to 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic acid (73) in 89% yield by refluxing with potassium hydroxide in 95% ethyl alcohol followed by acidification with dilute hydrochloric acid. Contrary to the $AX_2$ NMR pattern displayed by the methine and methylene protons in nitrile 65, acid 73 and ester 72 displayed complex multiplet patterns between its methine and methylene protons.

Conversion of acid 73 to the acid chloride with thionyl chloride followed by treatment of the acid chloride with ammonium hydroxide yielded in 79% 2-(3,4,5-trimethoxybenzyl)
-3,4-dibenzyloxyphenylacetic acid amide (74). The amide 74 was then reduced with diborane in THF to yield amine 45 in 44% yield.

Attempts at cyclizing 2-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)propylamine hydrochloride (66) with formalin according to Shamma and Hillman\textsuperscript{143} did not yield the desired cyclized product 68. A reaction spontaneously occurred upon addition of the formalin to an alcoholic solution of the amine hydrochloride 66 with the evolution of gas. Thin layer chromatography indicated the formation of several unidentifiable products which could not be isolated. Refluxing the mixture increased the number of products observed by chromatography. Treatment of 66 with formic acid according to the procedure of Koyama et al.\textsuperscript{144} also appeared to be unsuccessful in forming 68.

Formylation of the free base of 66 via a mixed anhydride of formic acid and ethyl chloroformate according to the procedure of Kaiser et al.\textsuperscript{145} appeared to be unsuccessful. However, formylation of amine 66 with chloral in chloroform and triethylamine according to Cheeseman and Greenberg\textsuperscript{146} cleanly produced the N-formyl intermediate as an oil. Its infrared (IR) spectrum displayed a very broad carbonyl stretch at 1675 cm\textsuperscript{-1}. Cyclization of the N-formyl intermediate by stirring in phosphorus oxychloride at 0-4\textdegree yielded the imine 67 which could be isolated from the reaction mixture in 45% yield as the hydrochloride salt.
This isolation was only accomplished by allowing 67 to slowly crystallize out of the acidified anhydrous reaction mixture dissolved in chloroform and equilibrating with ethyl ether in a saturated ether chamber. The resulting opaque semi-solid was recrystallized from methanol-ethyl ether to form light-yellow crystals. Attempts at purifying 67 from the reaction mixture by chromatography were unsuccessful.

Attempts at increasing the yield of 67 by introducing acetonitrile as the solvent or increasing the length of the reaction time were unsuccessful. Heating the reaction mixture produced none of the desired product 67.

Evidence for cyclization to 6,7-dibenzyloxy-4-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline hydrochloride (67) rather than to 5,6-dibenzyloxy-4-(3,4,5-trimethoxybenzyl)-3,4-dihydroisoquinoline hydrochloride may be found in the NMR spectrum. A spectrum of the free base of 67 in deuterated chloroform shows the two aromatic protons of the isoquinoline ring appearing as two singlets at δ 6.43 and 6.93. The proton at the 1-position appears as a broad singlet at δ 8.25. In a spectrum of the hydrochloride 67 in deuterated chloroform the two aromatic protons appear as singlets at δ 6.62 and 7.68, and the proton at the 1-position appears as a broad singlet at δ 9.18.

Reduction of the imine 67 with sodium borohydride in methanol yielded in 79% the 4-(3,4,5-trimethoxybenzyl)-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline isolated as the
hydrochloride salt 68. Removal of the benzyloxy protecting groups using catalytic hydrogenation afforded in 77% yield catechol 44. More directly, 44 could be obtained in 84% yield by catalytic hydrogenation of the imine hydrochloride 67.

Acetylation of the catecholic tetrahydroisoquinoline 44 yielded the triacetylated derivative 75 as indicated by an ester carbonyl at 1770 cm⁻¹ and an amide carbonyl at 1665 cm⁻¹ in the IR spectrum. A 90 MHz NMR spectrum in deuterated dimethyl sulfoxide at 305°K gave a complex spectrum due to a number of conformers present. As seen in Figure 2 increasing the temperature to 345° greatly simplified the spectrum by eliminating the various conformers of 75.

The norepinephrine analog, 2-(3,4-dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine hydrochloride (45), was obtained in 75% yield by catalytic hydrogenation of 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine hydrochloride (66).
Figure 2

90 MHz NMR Temperature Study of 1-(3,4,5-Trimethoxybenzyl)-2,6,7-triacetyl-1,2,3,4-tetrahydroisoquinoline
II. Synthesis of Fragmented Derivatives of Trimetoquinol (47-50; 51-54).

A. General Synthesis:

The general synthesis of the fragmented analogs of trimetoquinol (47-50) was accomplished through the key intermediate ketone 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a). Similarly, the synthesis of the benzyl analogs of this series has been accomplished through the intermediate ketone 1-(3,4-dibenzyloxyphenyl)-2-phenyl-ethanone (76b).

Initially the synthesis of the intermediate ketone 76a was approached through Friedel-Crafts acylations. Reaction of o-dibenzyloxybenzene (78) and 3,4,5-trimethoxyphenylacetic acid (78) with polyphosphoric acid (PPA) according to the method of Edwards et. al. produced none of the desired ketone 76a and appeared to partially cleave the benzyl protecting groups. The reaction of 3,4,5-trimethoxyphenylacetyl chloride (79) with catechol (80) in the presence of aluminum trichloride according to Finzi produced a complex mixture with none of the desired acylated product 81 present. Substituting boron tribromide for aluminum trichloride in the above reaction yielded mainly ester products.
In the benzyl series Friedel-Crafts reactions were also investigated as a means to prepare the intermediate ketone 76a. None of the desired acylated product, 1-(3,4-dibenzyloxyphenyl)-2-phenylethanone (76b), however, was observed when o-dibenzyloxybenzene (77) was allowed to react with phenylacetyl chloride (82) in the presence of either stannous chloride, thionyl chloride, or no catalyst. The acylated intermediate 2-phenyl-1-(3,4-dihydroxyphenyl)ethanone (83) was observed in trace amounts when phenylacetyl chloride (82) was allowed to react with catechol (80) in the presence of boron trifluoride and was isolated in 17% yield in the presence of aluminum trichloride. The catechol portion was then dibenzylated in 49% yield according to the method of Pines et al.¹⁴⁹ to obtain 1-(3,4-dibenzyloxyphenyl)-2-
After these unsuccessful attempts at the synthesis of the key intermediate 76a via Friedel Crafts reactions, our attention shifted to the synthesis of this compound via dithiane alkylation reactions as illustrated in Scheme 3.

Scheme 3

The 2-(3,4-dibenzyloxyphenyl)-1,3-dithiane (86) was easily prepared in high yield by refluxing in a Dean-Stark trap 3,4-dibenzyloxybenzaldehyde (59) with 1,3-propane di­thiol (85) in benzene containing a trace amount of p-toluene sulfonic acid, according to the method of Hylton and Bockel-
However, when dithiane $86$ was allowed to react with $n$-butyl lithium and either 3,4,5-trimethoxybenzyl chloride ($63$) or 3,4,5-trimethoxybenzyl bromide ($64$) according to the general method of Seebach$^{151}$ none of the desired product, 2-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxybenzyl)-1,3-dithiane ($87a$) was obtained. When bromide $64$ was used in the alkylation procedure a more complex product mixture was obtained.

Because of these initial results other bases were investigated. Using sodium hydride in DMF to form the anion of $86$ and allowing it to react with $63$ yielded only starting materials. Similarly, starting materials were obtained when triphenylmethyl lithium in glyme was used in the attempted alkylation of $85$. With $t$-butyl lithium, however, dithiane $85$ was alkylated with 3,4,5-trimethoxybenzyl chloride ($63$) to yield in 72% the alkylated dithiane $87a$. Interestingly, contrary to the yellow color commonly reported for the anions of dithianes in solution$^{151}$, the anion of $85$ generated at -$25\pm5^\circ$ in THF produced a deep blue-green solution.

Hydrolysis of dithiane $87a$ with mercuric oxide and mercuric chloride in aqueous methanol yielded in 62% the desired ketone 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone ($76a$).$^{151}$ Using aqueous acetonitrile as the solvent according to Tanaka and Torii$^{152}$ reduced the yield to 33%. Hydrolysis of $87a$ with mercuric oxide and boron trifluoride-etherate according to the method of Vedejs and
and Fuchs gave a mixture of the ketone 76a, starting material, and products which were difficult to purify. Hydrolysis with cupric oxide and cupric chloride in 99% aqueous acetone according to the method of Narask, Sahashita, and Mukaiyama also gave a crude hydrolysis product which was difficult to purify. None of the desired ketone 76a was obtained when 87a was hydrolyzed with ceric ammonium nitrate (CAN).

Ketone 76a could also be cleanly obtained without isolation of 87a. Hydrolysis of the crude alkylation mixture with mercuric chloride and mercuric oxide in a 6:5:2 mixture of methanol, acetonitrile, and water yielded a semi-solid product mixture. Recrystallization of this product with chloroform-ethyl ether yielded the desired ketone 76a in yields of up to 56% overall.

Similar alkylation of dithiane 85 with benzyl chloride yielded 80% 2-(3,4-dibenzyloxyphenyl)-2-benzyl-1,3-dithiane (87b). Hydrolysis of dithiane 87b with mercuric chloride and mercuric oxide in aqueous methanol yielded 1-(3,4-dibenzyloxyphenyl)-2-phenylethanone (76b) in 72% yield. Hydrolysis of the crude alkylation reaction mixture with mercuric chloride and mercuric oxide in a mixture of methanol, acetonitrile and water yielded an oily residue. Filtration of this residue through acidic alumina with benzene followed by concentration and addition of hexane yielded in 34% the ketone 76b.
The primary amine derivative, 1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (48) and its phenyl analog, 1-(3,4-dihydroxyphenyl)phenylethylamine hydrochloride (51) were prepared from the ketone intermediates 76a and 76b respectively as shown in Scheme 4.

Scheme 4

The oxime of 76a could not be formed with sodium carbonate and hydroxylamine in aqueous ethanol according to Inubushi and Fujitani due to the low solubility of the ketone 76a in ethanol. The O-methyl ether 88a, however, could be obtained in 87% yield from 76a by refluxing with methoxyamine hydrochloride in a pyridine-ethanol mixture according to the procedure of Feuer and Braunstein. The
methoxyamine derivative 88a was reduced to the primary amine 89a by refluxing in diborane-THF. The diborane complex was destroyed by refluxing in 30% aqueous potassium hydroxide and the product 89a was isolated as the hydrochloride salt in 84% yield. Hydrogenolysis of 1-(3,4-dibenzylxyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (89a) with 10% palladium on carbon afforded in 89% yield the catecholamine 48.

Similarly the ketone 76b was converted to the methoxyamine derivative 88b in 88% yield followed by conversion to the hydrochloride 89b in 86% yield. Hydrogenation of 89b with 10% palladium on carbon afforded in 85% yield the catecholamine, 1-(3,4-dibenzylxyloxyphenyl)phenethylamine hydrochloride (51).

The fragmented trimetoquinol derivative 47 along with derivatives 49 and 50 was prepared by the general reaction procedures described in Scheme 5.

![Scheme 5](attachment:image.png)
In initial studies the imine 90b could not be formed through a dehydration reaction in which the ketone 76a dissolved in benzene was stirred for 24 hours with anhydrous ethylamine over 3 Å or 5 Å molecular sieves. This observation, i.e., that the ketone system could readily form the oxime ether yet fail to form the imine derivative has been previously noted in similar systems. The ketone 76a, however, was converted to the desired imines 90a-c by allowing the appropriate alkylamine (methylamine, ethylamine, and isopropylamine) to react with 76a dissolved in benzene in the presence of titanium tetrachloride. Upon the addition of titanium tetrachloride the reaction mixtures became an intense red to brown color which changed to a yellow color upon completion of the reaction. The yellow solutions were filtered and the solvent and any excess amine were removed in vacuo to yield a mixture of the imines 90a-c and the unreacted ketone 76a. The imine rather than the enamine form is believed to be present since the imine form is known to predominate when a hydrogen would be present on the nitrogen of the enamine tautomer. The imine formation in
the crude reaction products of \textit{90a} and \textit{90b} could be observed by NMR spectroscopy by a shift of the methylene singlet and the appearance of \textit{syn-} and \textit{anti-}isomers. 161 Attempts at acquiring a quantitative conversion to the amine by the addition of excess amine or a slight excess of titanium tetrachloride were unsuccessful. The imine intermediates were unstable and hydrolyzed to starting material in the presence of water.

Reduction of the intermediate imines \textit{90a} and \textit{90b} was initially carried out using sodium borohydride in methanol. This procedure, however, was not successful in the reduction of the N-isopropyl derivative \textit{90c}. However, reduction in excess refluxing diborane-THF gave the desired amine which was isolated, with difficulty, as the hydrochloride salt \textit{91c}. The N-methyl imine \textit{90a} has been reduced by either method. Diborane reduction of the imines appears to be superior to the sodium borohydride reduction. Hydrogenolysis of the amine hydrochlorides \textit{91a-c} with palladium on carbon yielded the catecholamines \textit{47, 49, and 50}. The reaction yields obtained via Scheme 5 are summarized in Table I.
Table I

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Mp, °C</th>
<th>Solvent</th>
<th>Reducing Agent</th>
<th>Yield%</th>
</tr>
</thead>
<tbody>
<tr>
<td>91a</td>
<td>78-79^a</td>
<td>ethyl ether-ethanol</td>
<td>B(_2)H(_6)/THF</td>
<td>64b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NaBH(_4)/MeOH</td>
<td>32b</td>
</tr>
<tr>
<td>91b</td>
<td>188-189</td>
<td>ethyl ether-ethanol</td>
<td>B(_2)H(_6)/THF</td>
<td>64b</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>NaBH(_4)/MeOH</td>
<td>48b</td>
</tr>
<tr>
<td>91c</td>
<td>164-166</td>
<td>ethyl ether-ethanol</td>
<td>B(_2)H(_6)/THF</td>
<td>43b</td>
</tr>
<tr>
<td>49</td>
<td>145-149</td>
<td>ethyl ether-ethanol</td>
<td>-------</td>
<td>80</td>
</tr>
<tr>
<td>47</td>
<td>186-187</td>
<td>ethyl ether-ethanol</td>
<td>-------</td>
<td>89</td>
</tr>
<tr>
<td>50</td>
<td>171.5-172.5</td>
<td>ethyl ether-ethanol</td>
<td>-------</td>
<td>89</td>
</tr>
</tbody>
</table>

\(^{a}\) glass \(^{b}\) Overall from ketone 76a

In the benzyl series compounds 52-54 have been similarly prepared from the intermediate ketone 76b according to Scheme 6.

Scheme 6

\[
\begin{align*}
\text{BzI} & \quad \text{O} \\
\text{BzI} & \quad \text{O} \\
\text{76b} & \quad \text{TiCl}_4, \text{OH} \\
\text{NH}_2R & \quad \text{1. Reduction} \\
\text{BzI} & \quad \text{BzI} \\
\text{BzI} & \quad \text{NR} \\
\text{92a-c} & \\
\text{R= a= Me} & \\
\text{R= b= Et} & \\
\text{R= c= i-Pr} & \\
\downarrow & \\
\text{1. Reduction} & \\
\text{2. HCl} & \\
\text{93a-c} & 
\end{align*}
\]
The reaction yields obtained for compounds 93a-c, 52, 53, and 54 according to Scheme 6 are summarized in Table II.

Table II

<table>
<thead>
<tr>
<th>Compd.</th>
<th>Mp, °C</th>
<th>Solvent</th>
<th>Reducing Agent</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>93a</td>
<td>115-117</td>
<td>ethyl ether-ethanol</td>
<td>B₂H₆/THF</td>
<td>40ᵃ</td>
</tr>
<tr>
<td>93b</td>
<td>133-134</td>
<td>ethyl ether-ethanol</td>
<td>NaBH₄/MeOH</td>
<td>39ᵃ</td>
</tr>
<tr>
<td>93c</td>
<td>149.5-151.5</td>
<td>ethyl ether-ethanol</td>
<td>B₂H₆/THF</td>
<td>47ᵃ</td>
</tr>
<tr>
<td>52</td>
<td>182-185</td>
<td>ethyl ether-benzene-ethanol</td>
<td>----</td>
<td>80</td>
</tr>
<tr>
<td>53</td>
<td>182</td>
<td>ethyl ether-ethanol</td>
<td>----</td>
<td>88ᵇ</td>
</tr>
<tr>
<td>54</td>
<td>165-166</td>
<td>ethyl ether-ethanol</td>
<td>----</td>
<td>77</td>
</tr>
</tbody>
</table>

ᵃOverall from ketone 76b ᵇRef. 161

Unlike the trimethoxy analog 91c the benzyl isopropyl derivative 93c was readily formed by reduction of the intermediate imine 92c with sodium borohydride. Unlike 91c compound 93c could also be prepared from the primary amine 89b. Stirring the free base of 89b with acetone over molecular sieves followed by sodium borohydride reduction and hydrochloride salt formation afforded the isopropylamine 93c in 63 % yield.
B. Alternate Synthesis Leading to Compounds 47 and 49.

The acid, 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyl-oxy-phenylacetic acid (73), was readily converted to the intermediate isocyanate 94 through a modified Curtius rearrangement.\(^{162}\)

The intermediate isocyanate was then converted in 78% yield to the methyl carbamate 95a by stirring in anhydrous methanol. However, the methyl carbamate could not be hydrolyzed to the amine 89a by refluxing in a solution of 15% aqueous sodium hydroxide in methanol. Similarly the crude benzyl carbamate 95b could not be hydrolyzed to 89a by refluxing with either potassium hydroxide in 95% ethanol or with hydrazine. Reduction of the methyl carbamate 95a with lithium aluminum hydride in refluxing ethyl ether afforded the N-methyl amine 91a in 49% yield.
Reaction of isocyanate 94 with methyl lithium gave the desired amide 96 in 38% yield. Reduction of amide 96 with diborane in THF followed by isolation as the hydrochloride salt yielded the amine 91b.
In the mass spectra of compounds 47-50 none of the molecular ions of these compounds could be obtained with electron impact (EI) mass spectrometry. Instead, common fragmentation patterns were observed with m/e 303, 302 (major), and 287 being predominant. A possible general fragmentation pattern for these compounds is shown in Figure 3. With chemical ionization (CI) mass spectroscopy of compounds 48 and 49, however, the molecular ions could be obtained. Similar fragmentation patterns were also observed with m/e 303, 302, and 287 being present.

Acetylation of the N-methyl catecholamine 49 afforded the triacetylated derivative 97. NMR spectroscopy of this derivative dissolved in deuterated chloroform at 293 °K indicated the presence of two conformers in a ratio of 2:1. This ratio could not be significantly altered by cooling the solution to 223 °K. A single conformer, however, could be obtained when 97 was heated in deuterated dimethyl sulfoxide to 345 °K. (Figure 4)
Figure 3

Possible General Fragmentation Pattern for Compounds 47-50
Figure 4

90 MHz NMR Temperature Study of N-Methyl-N-acetyl-1-(3,4-diacetoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine
III. Synthesis of 3-(3,4-Dihydroxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (56) and the attempted synthesis of cis- and trans-2-(3,4-Dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)piperidine hydrochloride (57 and 58).

Refluxing 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (89a) with formalin according to the procedure of Shamma and Hillman\(^{143}\) yielded in 69% 3-(3,4-dibenzyloxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (99). Catalytic hydrogenolysis of the tetrahydroisoquinoline 99 then afforded the desired catechol 56.
Initial attempts at synthesizing cis- and trans-2-(3,4-dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)piperidine hydrochloride (57 and 58) involved the formation of the piperidine ring via an alkylation of the enamine 101 with 3-bromopropylamine hydrobromide (102) as reported by Hauck and Purcell.163

Allowing 1-(3,4-dibenzylxoxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) and piperidine (100) to react with titanium tetrachloride yielded crude enamine 101.164 However, upon heating the crude enamine 101 dissolved in dimethylformamide with 3-bromopropylamine hydrobromide (102) none of the desired imine 103 was obtained. Increasing the reaction time and temperature gave no indication of reaction.
Upon aqueous work-up only starting ketone 76a could be isolated.

Alkylation of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) with acrylonitrile in the presence of lithium diisopropylamide in THF yielded in 49% the monoalkylated product 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-cyanobutanone (104). It has been previously reported that the monoalkylation of deoxybenzoin systems with acrylonitrile proceeded only with sodium metal or triton B as the base. Using triton B with ketone 76a and acrylonitrile afforded only starting materials. With sodium hydride as the base only dialkylated product 105 was obtained in 63% yield.
The reaction of keto-nitrile 104 with potassium hydroxide in methanol-t-butyl alcohol according to the method of Campbell and Stevens 165 afforded none of the desired amide 106. Instead, only polymers were obtained.

Alternatively the synthesis of the similar amide 109 was approached according to Scheme 7.
Ketone 76a was alkylated with methyl acrylate in the presence of lithium diisopropylamide to yield 74% of the monoalkylated ester 107. Attempts at forming the O-methyl oxime 108 by refluxing 107 with methoxyamine hydrochloride in ethanol-pyridine, however, were unsuccessful. Similarly, amide 110 could not be successfully obtained by hydrolysis of the ester 107 followed by acid chloride formation and reaction with ammonium hydroxide. Hydrolysis appeared to give a very crude acid which afforded a large amount of polymer upon acid chloride formation.

Reduction of the keto-nitrile 104 with diborane yielded a crude intermediate amino-alcohol 111. Upon acidification under anhydrous conditions with ethyl ether saturated with anhydrous hydrogen chloride gas intermediate 111 formed two unidentifiable products. Acetylation of these products indicated the presence of both an amine and alcohol group. Refluxing the amino-alcohol 111 in xylene and p-toluene sulfonic acid according to the procedure of Bell et. al.166 failed to give the desired piperidine 112. Instead, only starting materials were obtained. Treatment of amino-alcohol 111 with thionyl chloride and aqueous base similar to the method of Glacet and Becue167 yielded mainly polymer.
Reduction of the keto-nitrile 104 with sodium borohydride followed by treatment with thionyl chloride and further reduction with diborane followed by quenching of the reaction with aqueous sodium hydroxide solution yielded an unknown product. Acetylation of this unknown product indicates the presence of an amine group.
B. BIOLOGICAL

Pharmacological studies of these compounds were carried out in the isolated β-adrenoceptor systems of guinea pig trachea, guinea pig atria and rat adipose tissue. In all biological systems the ED50 values represent the concentration of each agonist required to produce a response equal to one-half the maximal response produced by isoproterenol. Data are presented in terms of the mean pD2 value ± SE (standard error) obtained from cumulative dose-response curves in which the pD2 value is defined as -log ED50. Compounds eliciting a response of less than 50% were classified as weakly active while those having less than 10% activity were classified as inactive.

Guinea pig tracheal strips were mounted in a jacketed muscle chamber containing a modified Krebs solution. Muscle tone in each preparation was increased with 3 X 10^-7 M carbachol and cumulative dose-response curves were obtained for each drug. The individual plots of tracheal relaxation obtained with 10^-5 M isoproterenol added at the end of each experiment versus the log molar concentration were prepared and the ED50 values were individually determined. Dose-response curves were uncorrected for normal tracheal tone relaxation.

In the isolated atrial preparations, the atrium dissected from guinea pigs was placed in a jacketed muscle chamber
containing a modified Krebs solution. After equilibration
the atrium was exposed to test doses of the drugs and the
atrial rate was recorded. Chronotropic responses were
expressed in terms of the maximum response obtained in the
presence of \(10^{-5}\) M isoproterenol added at the end of each
experiment.

The lipolytic responses were measured in isolated fat
cells obtained by the method of Rodbell\textsuperscript{168} from the epididy-
mal fat tissues of non-fasted male Sprague-Dawley rats. The
amount of glycerol released was compared with a maximal
release of glycerol obtained in the presence of \(10^{-6}\) M
isoproterenol.

I. Biological Activity of 4-(3,4,5-trimethoxybenzyl)-6,7-
dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (44)
and 2-(3,4-dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)propyl-
amine hydrochloride (45).

The relative abilities of the 4-substituted analog 44
and the norepinephrine analog 45 to stimulate chronotropic
response and tracheal relaxation are summarized in Figure 5.
Clearly shifting the 1-arylmethyl group to the 4-position
resulted in compounds possessing smaller \(\text{pD}_2\) values than the
parent compound \(\text{d}l\)-trimetoquinol (\(\text{d}l\)-TMQ). Compound 45
which does not contain an intact tetrohydroisoquinoline ring
system possessed the lowest \(\text{pD}_2\) value for tracheal relaxation.

Interestingly the 4-substituted tetrahydroisoquinoline
44 was inactive in eliciting a chronotropic response in
Comparison of Trimetoquinol (dl-TMQ) and 4-Substituted Analogs in Guinea Pig Atria and Trachea. Values Plotted Represent the Mean pD₂ Value (-log ED₅₀) of N = 4-8 ± SE For Each Compound.
guinea pig atria. Therefore, although the relative potency of 44 is at least 100-fold less than dl-trimetoquinol in tracheal relaxation, it appears to be more selective for the β-adrenoceptor systems of trachea than atria.

In lipolysis the norepinephrine analog 45 was inactive. Compound 44 was not tested.

II. Biological Activity of the Fragmented Derivatives of Trimetoquinol (47-50; 51-54).

In the trimethoxy series all of the fragmented derivatives 47-50 possessed an ability to produce tracheal relaxation, chronotropic effects on the heart, and lipolysis. The relative abilities of each fragmented derivative 47-50 to stimulate chronotropic response and tracheal relaxation are summarized in Figure 6. All of the analogs possessed pD2 values which were smaller than the parent drug, dl-trimetoquinol, in both β-adrenoceptor systems. The N-methyl analog 49 was the most active of the synthesized analogs with the primary amine analog 48, N-ethyl analog 47 and N-isopropyl analog 50 being nearly equivalent as weak stimulants of both β-adrenoceptor systems. Although each analog along with dl-trimetoquinol possessed a greater pD2 value on atria than trachea no changes in the relative selectivity for these receptor systems was observed.

Data obtained for analogs 47-50 and dl-trimetoquinol on the release of glycerol from the isolated fat cells are presented in Figure 7. Clearly dl-trimetoquinol was more
Comparison of Trimetoquinol (dl-TMQ) and Fragmented Analogs in Guinea Pig Atria and Trachea. Values Plotted Represent the Mean pD$_2$ Value (-log ED$_{50}$) of N = 4-6 ± SE For Each Compound.
Figure 7

Dose-Response Curves For Trimetoquinol (dl-TMQ) and Fragmented Analogs on the Release of Glycerol From Epididymal Fat Cells. Values Plotted Represent the Mean Percent Lipolytic Response of N = 3 ± SE as Indicated by the Vertical Lines.
active than any of the analogs tested. Moreover, each of
the analogs was unable to exhibit a maximal rate of glycerol
release over the concentration range of $10^{-8}$-$10^{-4}$ M. Of
these analogs only the N-methyl derivative 49 showed signifi-
cant lipolytic activity at $10^{-6}$ M with the remaining analogs
47, 48 and 50 being only weakly active in this $\beta$-adrenoceptor
system.

These studies indicate that the intact tetrahydroiso-
quino line nucleus appears to be necessary for the potent $\beta$-
adrenoceptor action possessed by dl-trimetoquinol. Fragmenta-
tion of the intact tetrahydroisoquinoline ring between the
C$_4$ position and the aromatic ring leads to a considerable
reduction in $\beta$-adrenoceptor activity. (Compare dl-THQ and
47 in Figures 6 and 7) Of the synthesized analogs the N-
methyl analog 49 showed the greatest activity, although its
relative potency was at least 100-fold less in the $\beta$-adreno-
ceptor systems examined. It is believed that these compounds
are direct-acting $\beta$-adrenergic stimulants since the open-
chain analog 46 has been reported to be a direct-acting $\beta$-
adrenergic agonist.\textsuperscript{123}

To determine if a similar pattern of biological activ-
ity could be seen in the benzyl series, the biological act-
ivity of compounds 52-54 was compared with the activity of
1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (1-
Bz1-DiOH-THI). The relative ability of each fragmented
derivative to stimulate chronotropic response and bronchial
relaxation are summarized in Figure 8.

Unlike the trimethoxy series the presence of an intact tetrahydroisoquinoline nucleus is not a prerequisite for bronchial relaxant activity. Both the N-methyl analog \(52\) and the N-ethyl analog \(53\) possessed significant tracheal relaxant activity comparable to that of the parent tetrahydroisoquinoline. In chronotropic response, however, fragmentation greatly reduced the response observed. Compared to the intact tetrahydroisoquinoline, the N-ethyl analog \(53\) possessed significantly reduced activity while the N-isopropyl analog \(54\) and the N-methyl analog \(52\) were weakly active and inactive respectively.

Compounds \(53\) and \(54\) were also tested for their ability to elicit a lipolytic response. Both fragmented derivatives were inactive. From these results it can be suggested that compound \(52\) is probably also inactive in this \(\beta\)-adrenoceptor system.

In the benzyl series, the results indicate that fragmentation of the tetrahydroisoquinoline nucleus can lead to compounds that exhibit selective \(\beta\)-adrenergic activity.

III. Biological Activity of 3-(3,4-Dihydroxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (56).

This compound may be considered to be an analog of the fragmented derivative \(49\) in which the N-methyl group has been attached to the trimethoxyphenyl ring. This
Comparison of 1-Benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (1-Bzl-DiOH-THI) and Fragmented Analogs in Guinea Pig Atria and Trachea. Values Plotted Represent the Mean pD$_2$ Value (-log ED$_{50}$) of N = 4-6 ± SE For Each Compound.
compound has been found to be inactive in both its ability to release glycerol from fat cells and its ability to elicit a chronotropic response. Compound 56 was found to be weakly active in tracheal relaxation. A dose-response curve of compound 56 and the N-methyl derivative 49 is shown in Figure 9.

Dose-Response Curves For N-Methyl-1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine and 3-(3,4-Dihydroxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline in Guinea Pig Trachea. Values Plotted Represent the Mean Percent Tracheal Relaxation of \( N = 3 \) ± SE as Indicated by the Vertical Lines.
EXPERIMENTAL

Melting points were determined in open capillaries with a Thomas-Hoover Uni-Melt apparatus and are uncorrected. Infrared spectra were obtained with either a Perkin-Elmer Model 237 grating spectrophotometer or a Beckmann Model 33 or 4230 spectrophotometer. The NMR spectra were recorded with either a Varian A-60A NMR spectrophotometer at 60 MHz or a Bruker 6X 90E NMR spectrophotometer at 90 MHz. Unless specified all NMR spectra were recorded at 60 MHz. Mass spectra were obtained with a Dupont Model 21-491 double-focusing mass spectrometer with a Model 21-094 data system. Elemental analysis were determined by Galbraith Laboratories, Inc., Knoxville, Tenn.

Organic chemicals were obtained from Aldrich Chemical Company, Inc., Milwaukee, Wis.; Trans-World Chemicals, Washington, D. C.; and Eastman Kodak Company, Rochester, N. Y. Anhydrous methylamine gas was obtained from Matheson Company, Inc., Joliet, Ill. The reducing agents sodium borohydride, lithium aluminum hydride, and diborane, along with the methyl lithium, n-butyl lithium, t-butyl lithium, and sodium hydride bases and titanium tetrachloride were purchased from Ventron Corp., Alfa Products, Beverly, Mass. NMR solvents were purchased from Stohler Isotope Chemicals,
Waltham, Mass. Chromatographic separations were accomplished with thin layer chromatographic plates precoated with Silica Gel 60 F-254 at a thickness of 0.25 mm, preparative thin layer plates precoated with Silica Gel 60 F-254 at a thickness of 2 mm, Silica Gel 60 particle size 0.063-0.200 mm, and Aluminum Oxide, Acidic (Activity I). All were obtained from E. Merck, Darmstadt, Germany.

A. SYNTHETIC

3,4-Dibenzyloxybenzyl alcohol (60). To 3.0 g of lithium aluminum hydride suspended in 30 ml of tetrahydrofuran (THF) was added in 30 min 30.00 g (94.0 mmol) of 3,4-dibenzyloxybenzaldehyde (59) dissolved in 200 ml of THF. After stirring for 1 hr water was slowly added and the solution was filtered and extracted with ethyl ether. The ethereal layer was washed with 10% aqueous sodium hydroxide solution, dried over magnesium sulfate, filtered, and evaporated in vacuo. After recrystallization from chloroform-hexane 29.58 g (97.0%) of beige crystalline 60 mp 68-72° (lit 71-72°) was obtained. IR (NaCl, neat) 3300 cm⁻¹ broad OH. NMR (CDCl₃) δ 1.65 (s, 1H, OH), 4.53 (s, 2H, benzylic), 5.15 (s, 4H, -CH₂O-), 6.85-7.07 (m, 3H, aromatic), 7.23-7.53 (m, 10H, aromatic).

3,4-Dibenzyloxybenzyl Chloride (61).

Method A ¹³² - To a stirred suspension of 10.00 g (31.3 mmol)
of 3,4-dibenzylxybenzyl alcohol (60) and 4.0 g of sodium acetate in 500 ml of benzene was added 24 ml of thionyl chloride. After stirring at room temperature for 1 hr the solution was filtered and evaporated in vacuo to yield a dark solid. This was redissolved in benzene, boiled for 15 min with activated charcoal, and filtered. Evaporation of the benzene in vacuo and recrystallization from hexane yielded 8.65 g (81.5%) of gray chloride 61 mp 38-39° (lit mp 40° from benzene-light petroleum ether).

Method 133 - To a 500 ml round bottom flask was added 20.00 g (62.5 mmol) of 3,4-dibenzylxybenzyl alcohol (60) dissolved in 300 ml of anhydrous ethyl ether and 20 ml of thionyl chloride. After refluxing for 5 hr the solution was cooled, 3 g of activated charcoal was added, and the mixture was refluxed for 15 min. After filtration through a cone of magnesium sulfate, in vacuo evaporation of solvent, and recrystallization from ethyl ether-pentane 18.51 g (87.6%) of white 61 mp 43-44° was obtained. NMR (CDCl3) δ 4.47 (s, 2H, benzylic), 5.13 (s, 4H, -CH2O-), 6.87 (m, 2H, aromatic), 6.97 (m, 1H, aromatic), 7.17-7.53 (m, 10H, aromatic).

3,4-Dibenzylxybenzyl nitrile (62). This compound was synthesized from 3,4-dibenzylxybenzyl chloride (61) according to the method of Carlson and Lindquist.133 The product was filtered through acidic alumina and recrystallized from ethyl ether-pentane to yield in 79.0% white crystals.
mp 75-77° (lit 133 mp 80-81° from acetone-cyclohexane). IR (KBr) 2260 cm⁻¹ nitrile. NMR (CDCl₃) δ 3.6 (s, 2H, benzylic), 5.13 (s, 4H, -CH₂O⁻), 6.83-6.93 (m, 3H, aromatic), 7.30-7.50 (m, 10H, aromatic).

1-(3,4-Dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)-proprionitrile (65).

Method A - To a 250 ml 3-necked round bottom flask in an ice bath under argon was suspended 0.50 g of sodium hydride in 20 ml of dimethylformamide (DMF). To this was added over 30 min 5.00 g (15.2 mmol) of 3,4-dibenzyloxybenzyl nitrile (62) in 100 ml of DMF. The ice bath was removed and the mixture was stirred at room temperature for 4 hr. To the dark orange solution was then added over 15 min 3.30 g of 3,4,5-trimethoxybenzyl chloride (63) in 50 ml of DMF and stirring was continued for 15 hr. The mixture was then poured into 100 g of ice and extracted with benzene. The benzene layer was washed with water, saturated aqueous sodium chloride solution, dried over magnesium sulfate, and filtered. The benzene was then evaporated in vacuo and the remaining mixture was dissolved in 50 ml of ethyl ether. After slow evaporation at room temperature 2.10 g of crystalline 65 was obtained. The remaining mixture was placed on a 500 g silica gel column and eluted with 30:70 ethyl ether-pentane. The first fraction yielded 1.21 g (24.2%) unreacted 62 while the second fraction yielded an additional
1.13 g of 65 to give a total of 3.23 g (41.7%) of product mp 99.5-100.5° recrystallized from ethyl ether-acetone-pentane. A third fraction yielded 1.13 g (10.8%) of crude dialkylated product as an oil. IR (KBr) 2255 cm\(^{-1}\) nitrile. NMR (CDCl\(_3\)) \(\delta\) 3.01 (d, J=7 Hz, 2H, benzylic), 3.75 (s, 6H, methoxy), 3.82 (s, 3H, methoxy), 3.88 (t, J=7 Hz, 1H, Ar-CH-CN), 5.10 (s, 2H, -CH\(_2\)-O-), 5.13 (s, 2H, -CH\(_2\)-O-), 6.27 (s, 2H, aromatic), 6.77-6.90 (m, 3H, aromatic), 7.30-7.58 (m, 10H, aromatic).

Anal. calcd. for C\(_{32}\)H\(_{31}\)O\(_5\)N: C, 75.42; H, 6.13; N, 2.74. Found: C, 75.60; H, 6.16; N, 2.88.

Method B - In a 3-necked 250 ml round bottom flask under argon and cooled in an ice bath was generated in situ lithium diisopropylamide (LDA) by adding 9.5 ml of 1.67 M n-butyl lithium to 1.55 g of diisopropylamine. After 20 min the solution was cooled to -78° with a dry ice-acetone bath and 5.00 g (15.2 mmol) of nitrile 62 dissolved in 50 ml of freshly distilled THF was added with stirring. After 2.75 hr 3.30 g of 3,4,5-trimethoxybenzyl chloride (63) dissolved in 30 ml of THF and 0.6 g of hexamethylphosphoramide (HMPA) was added and the reaction mixture was allowed to go to room temperature. After 3 hr 5% aqueous hydrochloric acid was added and the product was extracted with ethyl ether. The ethereal layer was dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was redisolved in ethyl ether and allowed to slowly evaporate to
yield 3.44 g (44.7%) mp 99°. Chromatography of the remaining residue on silica gel with 1:3 ethyl acetate-light petroleum ether yielded 1.05 g (21.0%) of the starting nitrile 62.

3,4,5-Trimethoxybenzyl chloride (63). To an ice-cooled suspension of 10 g of sodium borohydride in 50 ml of methanol was added in 30 min 17.40 g (89.0 mmol) of 3,4,5-trimethoxybenzaldehyde (69) dissolved in 150 ml of methanol. The ice bath was removed and the solution was stirred at room temperature an additional 3 hr. The methanol was evaporated in vacuo, water was added, and the product was extracted with ethyl ether. After drying over magnesium sulfate, filtering, and removal of solvent in vacuo crude 3,4,5-trimethoxybenzyl alcohol (70) was obtained. IR (NaCl, neat) 3420 cm⁻¹ broad OH. NMR (CDCl₃) δ 2.00 (t, J=6 Hz, 1H, OH), 3.88 (s, 9H, methoxy), 4.63 (d, J=6 Hz, 2H, benzyl), 6.63 (s, 2H, aromatic). The crude product was dissolved in 100 ml of methylene chloride, ca 3 g of magnesium sulfate was added, and dry hydrogen chloride gas was bubbled for 5 min through the ice-cooled mixture. The solution was then washed with saturated aqueous sodium carbonate solution, saturated aqueous sodium chloride solution, and dried over magnesium sulfate. Upon filtration and concentration of solvent 14.90 g (77.0%) of the chloride mp 59-61° recrystallized from methylene chloride-hexane was obtained.
3,4,5-Trimethoxybenzyl bromide (64). This was prepared using hydrogen bromide gas by a method similar to the synthesis of the chloride 63. Clear needles mp 73.5-74.5° from methylene chloride were obtained in 77.8% yield (lit reported as oil). NMR (CDCl₃) δ 3.87 (s, 9H, methoxy), 4.45 (s, 2H, benzylic), 6.63 (s, 2H, aromatic).

2-(3,4-Dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine hydrochloride (66).

Method A - Under an argon atmosphere was refluxed 3.00 g (5.89 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)propynitrile (65) in 150 ml of THF and 25 ml of 1 M diborane. After 24 hr the solution was cooled and excess diborane was carefully decomposed with 10% aqueous potassium hydroxide. The mixture was then acidified with 10% aqueous hydrochloric acid and stirred at room temperature for several hours. The mixture was again made basic and extracted with ethyl ether and chloroform. The organic layers were combined, dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was redissolved in ca 50 ml of ethyl ether and 10 ml of anhydrous ethanol. Ethyl ether saturated with anhydrous hydrogen chloride was then added with stirring. The resulting gum was azeotroped.
with isopropyl alcohol and recrystallized from ethanol-ethyl ether to yield 2.73 g (84.3%) of the hydrochloride salt 66 mp 130°. IR, free base, (NaCl, neat) 3320 and 3380 cm⁻¹ N-H stretch. NMR, hydrochloride salt, (CDCl₃) δ 2.38-3.25 (m, 5H, methylene, methine, benzylic), 3.62 (s, 6H, methoxy), 3.73 (s, 3H, methoxy), 4.98 (s, 2H, -CH₂O-), 5.02 (s, 2H, -CH₂O-), 6.15 (s, 2H, aromatic), 6.67-6.88 (m, 2H, aromatic), 7.13-7.47 (m, 10H, aromatic). free base, (CDCl₃) δ 0.83-1.33 (m, 2H, NH₂ exchangeable with D₂O), 2.63-3.00 (m, 5H, methylene, methine, and benzylic), 3.72 (s, 6H, methoxy), 3.78 (s, 3H, methoxy), 5.10 (s, 4H, -CH₂O-), 6.17 (s, 2H, aromatic), 6.52-7.00 (m, 3H, aromatic), 7.17-7.65 (m, 10H, aromatic).

Anal. calcd. for C₃₂H₃₆O₅NCl: C, 69.87; H, 6.60; N, 2.55. Found: C, 70.18; H, 6.85; N, 2.43.

Method B - To 1.20 g (2.35 mmol) of 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzylxyloxyphenylacetic acid amide (74) dissolved in 100 ml of THF was added 15 ml of 0.9 M diborane. After refluxing under argon for 3 hr the solution was cooled and acidified with ethyl ether saturated with anhydrous hydrogen chloride gas. After stirring for 1 hr the solution was made basic with 10% aqueous potassium hydroxide solution and extracted with chloroform. After drying over magnesium sulfate and filtration, the chloroform was removed in vacuo. The residue was dissolved in 100 ml of ethyl ether containing ca 5 ml of ethanol and ethyl ether saturated with anhyd-
rous hydrogen chloride gas was added to yield 0.57 g (44.0%) of the hydrochloride salt \(^{66} \text{mp 130}^\circ\).

**Methyl-3,4-dibenzyloxyphenylacetate (71).** In a 100 ml round bottom flask 6.00 g (18.2 mmol) of 3,4-dibenzyloxybenzyl nitrile \(^{62}\) was refluxed for 24 hr in a solution containing 30 ml of methanol, 20 ml of dioxane, 10 g of potassium hydroxide and 10 ml of water. After in vacuo removal of solvent ethyl ether was added to the mixture and the acid was extracted with a saturated aqueous sodium bicarbonate solution. After acidification of the bicarbonate solution with dilute hydrochloric acid and extraction with ethyl ether the product was dried over magnesium sulfate. Upon filtration and removal of solvent 4.74 g of crude acid was obtained. Upon recrystallization from ethyl ether-pentane 4.38 g (69.0%) white needles \(^{132} \text{mp 107}^\circ\) was obtained (lit mp 109° from acetone-cyclohexane). IR (KBr) 2320-3300 cm\(^{-1}\) broad OH, 1785 cm\(^{-1}\) carbonyl. NMR (CDCl\(_3\)) \(\delta\) 3.50 (s, 2H, benzylic), 5.10 (s, 4H, -CH\(_2\)O-), 6.80-7.03 (m, 3H, aromatic), 7.17-7.58 (m, 10H, aromatic), 10.88 (broad singlet, 1H, CO\(_2\)H). The 3,4-dibenzyloxyphenylacetic acid was quantitatively esterified by stirring for 24 hr in a large excess of anhydrous methanol containing several drops of concentrated hydrochloric acid. After in vacuo removal of excess methanol the product was dissolved in ethyl ether, washed with saturated aqueous bicarbonate
solution, saturated aqueous sodium chloride solution and
dried over magnesium sulfate. After filtration and concen­
tration of the ethereal solution creamy-white crystals mp
41-42° (lit\textsuperscript{136} reported as oil bp\textsubscript{0.9} 189-190°) were obtained
upon freezing in a dry ice-acetone bath. IR (NaCl, neat)
1740 cm\textsuperscript{-1} carbonyl. NMR (CDCl\textsubscript{3}) \delta 3.42 (s, 2H, benzylic),
3.55 (s, 3H, O-methyl), 5.05 (s, 4H, -CH\textsubscript{2}O-), 6.57-6.93 (m,
3H, aromatic), 7.12-7.53 (m, 10H, aromatic).

Methyl-2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyl-\textit{ox}-
phenylacetate (72). Lithium diisopropylamide was generated
\textit{in situ} in a 100 ml 3-necked round bottom flask under argon
and cooled in an ice bath by adding to 1.12 g (11.0 mmol)
of diisopropylamine in 5 ml THF 8.3 ml of 1.67 M n-butyl
lithium. After 30 min a methanol-ice bath (-40°) was added
and 4.00 g (11.0 mmol) of methyl-3,4-dibenzylxyphenyl-
acetate dissolved in 11 ml of THF was added. One hour later
2.40 g (11.1 mmol) of 3,4,5-trimethoxybenzyl chloride (63)
dissolved in 0.66 g of HMPA and 10 ml of THF was added and
stirring was continued for 2 hr. Ethyl ether was added to
the mixture and the solution was washed with 10\% aqueous
hydrochloric acid, saturated aqueous bicarbonate solution,
and saturated aqueous sodium chloride solution, and dried
over magnesium sulfate. After filtration the solvent was
removed \textit{in vacuo} and the residue was dissolved in 50 ml of
anhydrous ethyl ether. Upon slow evaporation 5.30 g (88.4\%)
of white powdery product mp 80-81° was obtained. Upon re-
crystallization from ethyl ether-hexane product mp 93-94°
was obtained. IR (KBr) 1725 cm⁻¹ carbonyl. NMR (CDCl₃) δ
2.52-3.37 (m, 2H, methylene), 3.47-3.93 (m, 1H, methine),
3.60 (s, 3H, methoxy), 3.75 (s, 6H, methoxy), 3.82 (s, 3H,
methoxy), 5.13 (s, 4H, -CH₂O-), 6.28 (s, 2H, aromatic),
6.63-7.03 (m, 3H, aromatic), 7.23-7.60 (m, 10H, aromatic).

Anal. calcd. for C₃₃H₃₄O₇: C, 73.00; H, 6.30.
Found: C, 72.88; H, 6.30

2-(3,4,5-Trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic
acid (73). To a 1 liter round bottom flask was added 2.97 g
(5.48 mmol) of methyl-2-(3,4,5-trimethoxybenzyl)-3,4-
dibenzyloxyphenylacetate (72), 10 g of potassium hydroxide,
and 700 ml of 95% ethanol. After refluxing for 24 hr the
solvent was removed and the product dissolved in water. The
aqueous solution was washed with ethyl ether, acidified with
dilute hydrochloric acid, and extracted with ethyl ether.
The ether layer was washed with saturated aqueous sodium
chloride and dried over magnesium sulfate. After filtration
the ethyl ether was slowly evaporated to give a powdery
white product. Recrystallization from chloroform-ethyl
ether-pentane yielded 2.58 g (89.1%) of the acid 73 mp 104-
105°. IR (NaCl, neat) 3500 cm⁻¹ broad OH, 1760 and 1710
cm⁻¹ sharp carbonyls; (KBr) 3610-2400 cm⁻¹ broad OH, 1710
cm⁻¹ weak carbonyl. NMR (CDCl₃) δ 2.47-3.32 (m, 2H,
methylene), 3.45-3.88 (m, 1H, methine), 3.67 (s, 6H, methoxy), 3.77 (s, 3H, methoxy), 5.08 (s, 4H, \(-\text{CH}_2\text{O}-\)), 6.23 (s, 2H, aromatic), 6.83 (s, 2H, aromatic), 6.95 (s, 1H, aromatic), 7.20-7.55 (m, 10H, aromatic), 10.91 (broad singlet, 1H, \(\text{CO}_2\text{H}\)).

**Anal. calcd.** for \(\text{C}_{32}\text{H}_{32}\text{O}_7\): C, 72.71; H, 6.10.
**Found:** C, 72.45; H, 6.04.

2-(3,4,5-Trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic acid amide (74). To a 100 ml round bottom flask containing 1.00 g (1.89 mmol) of 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyloxyphenylacetic acid (73) was added 2 ml of thionyl chloride. After stirring for 15 min at room temperature excess thionyl chloride was removed in vacuo and the acid chloride formed (IR, NaCl, neat 1760 cm\(^{-1}\)) was dissolved in 25 ml of ethyl ether. The ethereal solution was then added to 50 ml of concentrated ammonium hydroxide and allowed to evaporate overnight. The remaining precipitate was filtered, washed with water and ethyl ether, and recrystallized from chloroform-ethyl ether to give 0.79 g (79.0%) product 74 mp 106-108°. IR (KBr) 3430, 3340 (shoulder), 3220 cm\(^{-1}\) NH\(_2\), 1665 cm\(^{-1}\) carbonyl. NMR (CDCl\(_3\)) \(\delta\) 2.73-3.53 (m, 3H, methylene and methine), 3.67 (s, 6H, methoxy), 3.75 (s, 3H, methoxy), 5.08 (s, 4H, \(-\text{CH}_2\text{O}-\)), 5.60 (broad singlet, 2H, amide), 6.22 (s, 2H, aromatic), 6.70-6.98 (m, 3H, aromatic), 7.18-7.53 (m, 10H, aromatic).
Anal. calcd. for C_{32}H_{33}O_{5}N・H_2O: C, 72.57; H, 6.66; N, 2.64. Found: C, 72.80; H, 6.41; N, 2.55.

4-(3,4,5-Trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinoline hydrochloride (67). To an ice-cooled 50 ml round bottom flask was added 1.00 g (1.82 mmol) of 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)propylamine hydrochloride (66) dissolved in 15 ml of chloroform, 2 ml of triethylamine, and 0.37 g of chloral dissolved in 5 ml of chloroform. After stirring for 20 min the mixture was refluxed for 1 min and evaporated in vacuo. The residue was dissolved in ethyl ether and filtered to remove triethylamine hydrochloride formed in the reaction. The ethereal layer was again evaporated in vacuo to yield a crude N-formyl intermediate as an oil. IR (NaCl, neat) 1675 cm^{-1} N-formyl. This intermediate was dissolved in 15 ml of phosphorus oxychloride and stirred at 4° for 1 hr. The phosphorus oxychloride was removed in vacuo and the residue was washed with 10% aqueous potassium hydroxide and extracted with chloroform. After drying over magnesium sulfate and filtering, the chloroform solution was concentrated in vacuo to ca 5 ml. Ethyl ether saturated with anhydrous hydrogen chloride gas was added to the chloroform solution and the desired product 67 was crystallized from the reaction mixture through equilibration in a saturated ethyl ether chamber. The yellow-opaque crystalline product was recrystallized from methanol-ethyl ether to give 460 mg (45.2%) of a
light yellow crystalline product mp 205-206°. IR (KBr) 2750-2380 cm⁻¹ broad, amine hydrochloride, 1650 cm⁻¹ C=NH−. NMR (CDCl₃) δ 2.51-2.83 (m, 2H, methylene), 2.95-3.30 (m, 1H, methine), 3.68-4.00 (m, 3H, methylene and C=NH− which was exchangeable with D₂O), 3.82 (s, 9H, methoxy), 5.12 (s, 2H, -CH₂O−), 5.23 (s, 2H, -CH₂O−), 6.25 (s, 2H, aromatic), 6.62 (s, 1H, aromatic), 7.20-7.55 (m, 10H, aromatic), 7.68 (s, 1H, aromatic), 9.18 (broad singlet, 1H, -CH=N).

Anal. calcd. for C₃₃H₃₄O₅HCl: C, 70.77; H, 6.12; N, 2.50. Found: C, 70.76; H, 6.12; N, 2.45.

4-(3,4,5-Trimethoxybenzyl)-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (68). In a 250 ml round bottom flask was dissolved with heating 300 mg (0.54 mmol) of 4-(3,4,5-trimethoxybenzyl)-6,7-dibenzyloxy-3,4-dihydroisoquinoline (67) in 100 ml of methanol. To the cooled solution was added 500 mg of sodium borohydride and the solution was stirred for 3 hr. The solvent was removed in vacuo, water was added, and the product was extracted with chloroform. The chloroform solution was dried over sodium sulfate, filtered, and evaporated in vacuo. The residue was dissolved in ethyl ether and converted to the hydrochloride salt by the addition of ethyl ether saturated with anhydrous hydrogen chloride gas. Recrystallization from methanol-ethyl ether yielded 238 mg (79.1%) of a fluffy white product mp 243-244°. IR hydrochloride salt (KBr)
2840-2300 cm$^{-1}$ series of peaks indicative of hydrochloride salt; free base (NaCl, neat) 3340 cm$^{-1}$ NH. NMR (CDCl$_3$, 90 MHz) $\delta$ 1.79 (broad singlet, 1H, NH exchangeable with D$_2$O), 2.64-3.03 (m, 5H, methylene and methine), 3.79 (s, 6H, methoxy), 3.82 (s, 3H, methoxy), 3.85 (s, 2H, methylene at 1 position), 5.03 (s, 2H, -CH$_2$O-), 5.10 (s, 2H, -CH$_2$O-), 6.33 (s, 2H, aromatic), 6.59 (s, 1H, aromatic), 6.63 (s, 1H, aromatic), 7.21-7.51 (m, 10H, aromatic). Mass Spectrum (EI) m/e 525.

Anal. calcd. for C$_{33}$H$_{36}$O$_5$NCl: C, 70.5; H, 6.46; N, 2.49. Found: C, 70.43; H, 6.55; N, 2.42

4-(3,4,5-Trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (44).

Method A - A solution containing 100 mg (0.18 mmol) of 4-(3,4,5-trimethoxybenzyl)-6,7-dibenzyl oxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (68) dissolved in 100 ml of anhydrous ethanol and 25 mg of 10% palladium on carbon catalyst was hydrogenated at 40 psi for 8 hr. The solution was gravity filtered, concentrated in vacuo and allowed to crystallize in a saturated ethyl ether chamber. After recrystallization from methanol-ethyl ether 53 mg (76.6%) of an off-white crystal mp 264-265° was obtained. The product gave a positive ferric chloride test. IR (KBr) 3480 cm$^{-1}$ phenolic OH, 3160-2310 cm$^{-1}$ series of peaks indicative of an amine hydrochloride. Mass Spectrum (EI)
m/e 306.

Anal. calcd. for C$_{19}$H$_{24}$O$_5$NCl(·CH$_3$OH): C, 58.04; H, 6.82; N, 3.38. Found: C, 58.00; H, 6.46; N, 3.49.

**Method B** - A solution containing 200 mg (0.36 mmol) of 4-(3,4,5-trimethoxybenzyl)-6,7-dibenzylxyloxy-3,4-dihydroisoquinoline hydrochloride (67) dissolved in 250 ml of anhydrous ethanol and 100 mg of 10% palladium on carbon catalyst was hydrogenated overnight at 48 psi. The solution was gravity filtered, concentrated *in vacuo* and filtered through a cotton plug. The solution was further concentrated to ca 3 ml under a stream of argon and allowed to crystallize in a saturated ethyl ether chamber. After recrystallization from methanol-ethyl ether 136 mg (83.6%) of off-white product mp 264-265° was obtained.

A triacetylated derivative 75 was obtained by stirring overnight 56 mg (0.14 mmol) of 44 with a solution containing 2 ml of pyridine and 2 ml of acetic anhydride. The solution was evaporated *in vacuo* and stirred 1 hr with 10% aqueous hydrochloric acid. The product was then extracted with chloroform, washed with saturated aqueous sodium bicarbonate, dried over magnesium sulfate, filtered, and evaporated *in vacuo* to yield an oil. IR (NaCl, neat) 1770 cm$^{-1}$ ester carbonyl, 1665 cm$^{-1}$ amide carbonyl. NMR (DMSO-d$_6$, 345°K, 90 MHz) δ 2.03 (s, 3H, NAc), 2.23 (s, 3H, OAc), 2.24 (s, 3H, OAc), 2.60-2.83 (m, 2H, methylene), 3.01-3.35 (m, 1H, methine), 3.54 (s, 2H, methylene), 3.66
(s, 3H, methoxy), 3.75 (s, 6H, methoxy), 4.28-4.88 (m, 2H, methylene), 6.53 (s, 2H, aromatic), 7.08 (s, 2H, aromatic).

o-Dibenzyloxybenzene (77). This compound mp 59° (lit mp 60.5-61.5°) was prepared in 68% yield according to Pines et al. [148] NMR (CDCl₃) δ 5.17 (s, 4H, -CH₂O-), 6.95 (s, 4H, aromatic), 7.25-7.52 (m, 10H, aromatic).

2-Phenyl-1-(3,4-dihydroxyphenyl)ethanone (83). To a solution at 50° containing 3.00 g (27.3 mmol) of catechol (80) and 4.00 g of phenylacetyl chloride (82) dissolved in 100 ml of methylene dichloride was added in 10 min 7.67 g of aluminum trichloride. After further heating for 5 min the mixture was poured into 100 g of ice dissolved in 100 ml of 50% aqueous hydrochloric acid. The mixture was heated until all of the salt dissolved. The organic layer was then washed with water and extracted with saturated aqueous sodium bicarbonate solution. Acidification of the bicarbonate solution with dilute hydrochloric acid followed by filtration and recrystallization from chloroform-hexane yielded 2.23 g (17.9%) of brown powdery mp 169-171° (lit mp 173). IR (NaCl, nujol) 3500 cm⁻¹ phenolic OH, 1680 cm⁻¹ carbonyl. NMR (DMSO-d₆) δ 4.23 (s, 2H, benzylic), 6.66-6.98 (m, 2H, aromatic), 7.08-7.65 (m, 6H, aromatic).
2-Phenyl-(3,4-dibenzyloxyphenyl)ethanone (76b).

Method A - To a solution of 1.00 g (4.39 mmol) of catechol and 1.58 g of potassium carbonate in 160 ml of anhydrous acetone was added in 30 min 1.52 g of benzyl chloride (84). The solution was then refluxed under nitrogen for 24 hr. After filtration the solvent was removed in vacuo and the residue was dissolved in chloroform. Upon addition of light petroleum ether 0.88 g (49.0%) of ketone mp 87-89° was obtained.

Method B - To a 250 ml flask equipped with a magnetic stirrer were added 1.00 g (2.00 mmol) of 2-(3,4-dibenzyloxyphenyl)-2-benzyl-1,3-dithiane (87b), 0.90 g of red mercuric oxide, 2.20 g of mercuric chloride, 1.50 ml of methanol and 10 ml of water. After refluxing the mixture for 5 hr and filtration the solvent was removed in vacuo. The residue was dissolved in ethyl ether, washed with saturated ammonium chloride, and dried over magnesium sulfate. After solvent concentration and the addition of petroleum ether bp 39-60°, 0.59 g (71.9%) of crystalline ketone mp 91.5-92° was obtained. IR (KBr) 1665 cm⁻¹ carbonyl. NMR (CDCl₃) δ 4.15 (s, 2H, benzylic), 5.15 (s, 2H, -CH₂O-), 5.20 (s, 2H, -CH₂O-), 6.83-7.70 (m, 18H, aromatic).

Anal. calcd. for C_{28}H_{24}O_{3}: C, 82.33; H, 5.92.

Found: C, 82.47; H, 6.00.

Method C - In a 1 liter 3-necked jacketed reaction flask was added 20.00 g of 2-(3,4-dibenzyloxyphenyl)-1,3-dithiane (86)
dissolved in 500 ml of freshly distilled THF. After cooling to -25±5°, 35 ml of 2M t-butyl lithium was added over 30 min and the solution was stirred an additional 6 hr. To the dark green solution was then added 10.0 g of benzyl chloride (84) and the solution was stirred at room temperature overnight. The reaction mixture was acidified with 10% aqueous hydrochloric acid and extracted with ethyl ether. The ether layer was washed with saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution and evaporated in vacuo. The residue was redissolved in 500 ml of acetonitrile, 800 ml of methanol and 500 ml of water. Upon the addition of 7.7 g of mercuric chloride and 17.2 g of mercuric oxide the stirred solution was refluxed for 5 hr and filtered. The filtrate was evaporated in vacuo and redissolved in benzene. The benzene solution was then filtered through acid-washed alumina. Evaporation of the benzene in vacuo followed by recrystallization from ethyl ether-light petroleum ether yielded 6.80 g (34.0%) of ketone 76b mp 91-92°.

2-(3,4-Dibenzyloxyphenyl)-1,3-dithiane (86). To a 250 ml round bottom flask equipped with a Dean-Stark trap was placed 14.65 g (45.0 mmol) of 3,4-dibenzyloxybenzaldehyde (59), 5.0 g of 1,3-propanedithiol (85), a crystal of p-toluene sulfonic acid and 150 ml of benzene. The mixture was refluxed until the appropriate amount of water was re-
moved. The benzene solution was then cooled, washed with a saturated sodium bicarbonate solution, water, and dried over sodium sulfate. After filtration, evaporation and recrystallization from acetone-hexane 7.62 g (95.5%) of white needles mp 109-110° was obtained. NMR (CDCl₃) δ 1.67-2.25 (m, 2H, S-CH₂-CH₂-CH₂-S); 2.80-3.13 (m, 4H, S-CH₂-CH₂-CH₂-S), 5.08 (s, 1H, 2-position H), 5.10 (s, 2H, -CH₂O-), 5.13 (s, 2H, -CH₂O-), 6.77-7.62 (m, 13H, aromatic).

Anal. calcd. for C₂₂H₂₄O₂S₂: C, 70.55; H, 5.92; O, 7.83; S, 15.69. Found: C, 70.78; H, 5.92; O, 7.67; S, 15.71.

2-(3,4-Dibenzyloxyphenyl)-2-(3,4,5-trimethoxybenzyl)-1,3-dithiane (87a). To a flame dried 1 liter jacketed reaction flask equipped with a magnetic stirrer and under an argon atmosphere was added 30.00 g (73.4 mmol) of 2-(3,4-dibenzyloxyphenyl)-1,3-dithiane (86) dissolved in 600 ml of freshly distilled THF. After cooling to -25±5° an equimolar amount of t-butyl lithium was added to the stirred solution in 30 min. After 18 hr 16.05 g of 3,4,5-trimethoxybenzyl chloride (63) dissolved in 125 ml of THF was added and stirring was continued for 12 hr. Water was cautiously added as the reaction was warmed to room temperature. Ethyl ether was added to the solution and the ethereal solution was was washed with 10% aqueous hydrochloric acid. After drying over magnesium sulfate and filtration the solvent was removed in vacuo. The oily residue was placed
on a 2 kg silica gel column and eluted with benzene to give 9.33 g (22.9 mmol) of the starting dithiane (86), Rf 0.6 and 21.50 g (72.1% calculated from reacted 86) of the alkylated product 87a, Rf 0.4, as a golden oil. After stripping the column with chloroform 2.00 g of the ketone 76a (7.9%) was also obtained. NMR (CDCl₃) δ 1.66-2.03 (m, 2H, S-CH₂-CH₂-S), 2.33-2.70 (m, 4H, S-CH₂-CH₂-CH₂-S), 3.07 (s, 2H, benzylic), 3.57 (s, 6H, methoxy), 3.73 (s, 3H, methoxy), 5.03 (s, 2H, -CH₂O-), 5.13 (s, 2H, -CH₂O-), 5.85 (s, 2H, aromatic), 6.75-7.58 (m, 13H, aromatic).

Anal. calcd. for C₃₄H₃₆O₅S₂: C, 69.36; H, 6.16.
Found: C, 69.60; H, 6.26.

1-(3,4-Dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a).

Method A - To a 1 liter round bottom flask equipped with a magnetic stirrer was added 10.00 g (17.0 mmol) of 2-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxybenzyl)-1,3-dithiane (87a), 8.5 g of red mercuric oxide, 21.0 g of mercuric chloride, 700 ml of water and 800 ml of methanol. The stirred solution was refluxed for 5 hr. After filtration the methanolic solvent was removed in vacuo. The residue was dissolved in chloroform, washed with saturated aqueous ammonium chloride solution, and dried over magnesium sulfate. After filtration the chloroform was removed under vacuum to give a crude yellow product. Upon recrystallization from
chloroform-ethyl ether 5.20 g (61.5%) of white crystals mp 141.5-142.5° was obtained. IR (KBr) 1675 cm\(^{-1}\) carbonyl. NMR (CDCl\(_3\)) \(\delta\) 3.78 (s, 6H, methoxy), 3.80 (s, 3H, methoxy), 4.10 (s, 2H, benzylic), 5.17 (s, 2H, \(-\text{CH}_2\text{O}-\)), 5.20 (s, 2H, \(-\text{CH}_2\text{O}-\)), 6.45 (s, 2H, aromatic), 6.83-7.67 (m, 13H, aromatic).

**Anal. calcd. for C\(_{31}\)H\(_{30}\)O\(_6\):** C, 74.68; H, 6.07.

**Found:** C, 74.43; H, 5.98.

**Method B** - To a 3-necked 1 liter jacketed reaction flask equipped with a magnetic stirrer and under an argon atmosphere was added 25.00 g (61.2 mmol) of 2-(3,4-dibenzylxoy-phenyl)-1,3-dithiane (86) dissolved in 500 ml of THF. After cooling to -25±5° an equimolar amount of \(\text{t}-\text{butyl lithium}\) was added over 30 min. After 1 hr 16.05 g of 3,4,5-tri-methoxybenzyl chloride (63) dissolved in 100 ml of THF was added over 1 hr and the solution was stirred at room temperature overnight. The reaction mixture was then acidified with 10% aqueous hydrochloric acid and extracted with ethyl ether. The ethereal layer was washed with saturated aqueous sodium bicarbonate solution, saturated aqueous sodium chloride solution and evaporated in vacuo. The residue was dissolved in a solution of 500 ml of acetonitrile, 600 ml of methanol and 200 ml of water. Upon addition of 10.0 g of mercuric oxide and 17.1 g of mercuric chloride the stirred mixture was refluxed for 5 hr and filtered while still hot. The filtrate was evaporated in vacuo and the residue was redissolved in chloroform. The chloroform layer was washed
with saturated aqueous ammonium chloride solution and distilled water and dried over magnesium sulfate. In vacuo evaporation of the chloroform followed by recrystallization from ethyl ether-light petroleum ether yielded 17.10 g (56.1%) of ketone 76a mp 141-142°.

2,(3,4,5-Trimethoxyphenyl)-1-(3,4-dibenzyloxyphenyl)-ethylhydroxylimine methyl ether (88a). Into a 50 ml round bottom flask equipped with a magnetic stirrer were added 1.56 g (3.13 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl) ethanone (76a), 0.27 g (3.24 mmol) of methoxyamine hydrochloride, 10 ml of absolute ethanol, and 10 ml of pyridine. After refluxing the mixture for 24 hr the ethanol-pyridine was removed in vacuo to give a white solid. After recrystallization from ethanol 1.43 g (86.7%) of a white crystalline material, mp 91.5-92.5° was obtained. IR (KBr) 1585 cm⁻¹ C=N, 1005 cm⁻¹ NOCH₃. NMR (CDCl₃) δ 3.73 (s, 6H, methoxy), 3.80 (s, 3H, methoxy), 3.98 and 4.00 (both singlets, 5H total, benzylic and NOCH₃), 5.12 (s, 4H, -CH₂O-) 6.40 (s, 2H, aromatic), 6.75-7.55 (m, 13H, aromatic).

Anal. calcd. for C₃₂H₃₃O₆N: C, 72.85; H, 6.30; N, 2.65.
Found: C, 72.79; H, 6.29; N, 2.56.

2-(3,4,5-Trimethoxyphenyl)-1-(3,4-dibenzyloxyphenyl)-ethylamine hydrochloride (89a). To a 100 ml 2-necked round bottom flask equipped with a magnetic stirrer and under an
argon atmosphere was added 1.00 g (1.90 mmol) of 2-(3,4,5-
trimethoxyphenyl)-1-(3,4-dibenzyloxyphenyl)ethylhydroxyl-
imine methyl ether (88a) in 50 ml of THF and 10 ml of 0.9 M
diborane. After refluxing for 12 hr water was cautiously
added to the cooled solution to destroy excess diborane.
This was followed by the addition of 20 ml of 20% aqueous
potassium hydroxide and refluxing for an additional 12 hrs.
The amine was extracted with ethyl ether and dried over mag-
nesium sulfate. Upon filtration the solvent was removed in
vacuo to give a golden oil. Addition of the oil to ethyl
ether saturated with hydrogen chloride gas gave 0.85 g
(83.7%) of the desired amine hydrochloride mp 225-227° (re-
crystallized from ethyl ether-ethanol). IR free base (KBr)
3240 and 3340 cm⁻¹ primary NH₂. Salt (KBr) 2200-3300 cm⁻¹
broad NH₂ indicative of hydrochloride salt. NMR free base
(CDCl₃) δ 1.48 (s, 2H, NH₂ removed with D₂O), 2.55-2.90 (m,
2H, methylene), 3.78 (s, 6H, methoxy), 3.81 (s, 3H, meth-
oxy), 3.92-4.37 (m, 1H, methine), 5.13 (s, 4H, -CH₂O-), 6.32
(s, 2H, aromatic), 6.80-7.60 (m, 13H, aromatic).

Anal. calcd. for C₃₁H₃₄NO₅Cl:  C, 69.44; H, 6.40; N,
2.61. Found:  C, 69.20; H, 6.45; N, 2.47.

1-(3,4-Dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)-
etethylamine hydrochloride (48). A solution containing
300 mg (0.56 mmole) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-
trimethoxyphenyl)ethylamine hydrochloride (89a) in 150 ml
of absolute ethanol and 30 mg of 10% palladium on carbon catalyst was hydrogenated for 8 hr at 40 psi. To the solution was added ethanol saturated with hydrogen chloride gas and the mixture was concentrated in vacuo to a volume of ca 2 ml. After the addition of a small amount of ethyl ether (ca 10 ml) the solution was placed in a saturated ethyl ether chamber. Upon slow crystallization 178 mg (89.4%) of the catecholamine mp 186-187° were obtained. The material gave a positive ferric chloride test. IR (KBr) 3660-3320 cm⁻¹ broad O-H, 3320-2140 cm⁻¹ broad hydrochloride salt band, 1600 cm⁻¹ primary N-H. Mass Spectrum CI (iso-butane) m/e 303; EI m/e 303, 302, 288, 287.

Anal. calcd. for C₁₇H₂₂NO₅Cl: C, 57.36; H, 6.24; N, 3.94. Found: C, 57.48; H, 6.30; N, 3.86.

2-Phenyl-1-(3,4-dibenzyloxyphenyl)ethylhydroxylimine methyl ether (88b). Into a 50 ml round bottom flask equipped with a magnetic stirrer were added 1.28 g (3.13 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-phenylethanone (76b), 0.27 g (3.24 mmol) of methoxyamine hydrochloride, 10 ml of absolute ethanol, and 10 ml of pyridine. After refluxing the mixture for 20 hr the ethanol-pyridine was removed in vacuo to give a crude solid. Recrystallization from ethanol gave 1.05 g (87.6%) of product as white plates mp 101-101.5°. IR (KBr) 1600 cm⁻¹ C=N, 1035 cm⁻¹ NOCH₃. NMR (CDCl₃) δ 3.96 (s, 3H, methoxy), 4.02 (s, 2H, methylene), 5.07 (s, 4H,
-CH₂O-), 6.68-7.47 (m, 18H, aromatic).

**Anal. calcd. for C₂₉H₂₇O₃N:**  C, 79.61; H, 6.22; N, 3.20. **Found:**  C, 79.91; H, 6.36; N, 3.08.

**1-(3,4-Dibenzyloxyphenyl)-2-phenylethylamine hydrochloride (89b).** To a 250 ml 2-necked round bottom flask equipped with a magnetic stirrer and under an argon atmosphere were added 2.00 g (4.57 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-phenylethylhydroxylimine methyl ether (88b) dissolved in 100 ml of THF and 20 ml of 0.9 M diborane. After refluxing for 12 hr water was cautiously added to the cooled solution to destroy the excess diborane. Then 20 ml of 20% aqueous potassium hydroxide was added and the solution was refluxed again for 12 hr. This was followed by a continuous extraction with ethyl ether. The ethereal solution was dried over magnesium sulfate, filtered, concentrated **in vacuo**, and added to ethyl ether saturated with hydrogen chloride gas to give 1.75 g (85.5%) of the amine hydrochloride (89b) mp 187-188°C (recrystallized from ethyl ether-ethanol). **IR hydrochloride salt (KBr)** 2310-3150 cm⁻¹ broad, 2000 cm⁻¹ salt. **Free base (NaCl, neat)** 3260, 3350 cm⁻¹ primary NH₂. **NMR free base (CDCl₃)** 8 1.48 (broad s, 2H, NH₂ removed with D₂O), 2.50-3.12 (m, 2H, methylene), 3.87-4.25 (m, 1H, methine), 5.10 (s, 4H, -CH₂O-), 6.67-7.57 (m, 18H, aromatic).
Anal. calcd. for C_{26}H_{28}O_{2}NCl: C, 75.40; H, 6.33; N, 3.14. Found 75.64; H, 6.20; N, 3.23.

1-(3,4-Dihydroxy)phenethylamine hydrochloride (51).
A solution containing 500 mg (1.12 mmol) of 1-(3,4-dibenzyl-oxyphenyl)phenethylamine hydrochloride (89b) in 150 ml of absolute ethanol and 50 mg of 10% palladium on carbon catalyst was hydrogenated for 12 hr at 40 psi. After the addition of 2 ml of ethanol saturated with hydrogen chloride gas the solution was gravity filtered through 2 sheets of filter paper and concentrated in vacuo to a volume of ca 3 ml. After the addition of ca 10 ml of ethyl ether the solution was placed in a saturated ethyl ether chamber. Slow crystallization yielded 254 mg (85.2%) of the catecholamine hydrochloride mp 180.5-181.5°. The product gave a positive ferric chloride test. IR (KBr) 2100-3550 cm\(^{-1}\) broad. Mass Spectrum EI m/e 212, 165, 138.

Anal. cacld. for C_{14}H_{16}O_{2}NCl: C, 63.28; H, 6.07; N, 5.27. Found: C, 63.11; H, 5.94; N, 5.08.

N-Methyl-1-(3,4-dibenzyl-oxyphenyl)-2-(3,4,5-trimethoxy-phenyl)ethyamine hydrochloride (91a).
Method A - To a 250 ml 3-necked flask equipped with a magnetic stirrer and under an argon atmosphere was added 1.00 g (2.01 mmol) of 1-(3,4-dibenzyl-oxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) dissolved in 200 ml of benzene dried over sodium wire. After cooling the solution with an
ice bath. 0.35 g of titanium tetrachloride was added followed by the bubbling of anhydrous methylamine through the solution for 15 min. The solution changed from reddish-brown to a rose-orange. After 24 hrs the solution (yellow) was filtered and the solvent was removed in vacuo. The crude Schiff-base obtained as an oil (IR, NaCl, neat, 1635 cm⁻¹) was dissolved in 150 ml of anhydrous THF and transferred to a 2-necked 250 ml flask under argon. After the addition of 10 ml of 0.9 M diborane the mixture was refluxed for 10 hr. After cooling 50 ml of 10% aqueous sodium hydroxide solution was added to the reaction mixture and the solution was further refluxed for 10 hr. After cooling the product was extracted with ethyl ether, dried over magnesium sulfate, filtered, and the solvent was removed in vacuo. The residue was dissolved in ca 10 ml of ethanol and ethyl ether saturated with anhydrous hydrogen chloride gas was added with stirring. Upon cooling and filtration 700 mg (63.5%) of the amine hydrochloride mp 74-76° (recrystallized from ethyl ether-ethanol) was obtained. Upon drying under high vacuum at 78° a glass mp 78-79° was obtained. IR free base (NaCl, neat) 3310 cm⁻¹ N-H. Hydrochloride salt (KBr) 2700, 2950, 3450 cm⁻¹ all very broad indicative of hydrochloride salt. NMR free base (CDCl₃) δ 1.80 (s, 1H, NH, removed with D₂O), 2.20 (s, 3H, N-CH₃), 2.80 (d, J=7 Hz, 2H, benzyl), 3.12 (t, J=7 Hz, 1H, methine), 3.78 (s, 6H, methoxy), 3.82 (s, 3H, methoxy), 5.15 (s, 4H, -CH₂O-), 6.28 (s, 2H, aromatic),
6.80 (m, 3H, aromatic), 7.27-7.63 (m, 10H, aromatic).

Anal. calcd. for C_{32}H_{36}O_{5}NCl: C, 69.87; H, 6.60; N, 2.55. Found: C, 69.72; H, 6.68; N, 2.63.

Method B - In a 100 ml round bottom flask was refluxed 0.50 g (0.92 mmol) of methyl-N-[1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethyl]carbamate (96) dissolved in 50 ml of THF and 0.3 g of lithium aluminum hydride. After refluxing for 48 hr water was slowly added and the solution was filtered. The filtrate was extracted with ethyl ether and the ethereal layer was washed with 10% aqueous sodium hydroxide solution, dried over magnesium sulfate, filtered and evaporated in vacuo. The residue was dissolved in ethanol and ethyl ether saturated with anhydrous hydrogen chloride gas was added to yield 0.25 g (49.2%) of the hydrochloride salt, mp 77°.

N-Ethyl-1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (91b).

Method A - To a 1 liter 3-necked round bottom flask equipped with a magnetic stirrer and under an argon atmosphere was added 3.00 g (6.0 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) dissolved in 500 ml of dry benzene. After cooling the solution with an ice bath 10 ml of anhydrous ethylamine was added followed by 0.90 g of titanium tetrachloride. The solution immediately became reddish-orange in color. Continued stirring for 24 hr at
room temperature gave a yellow solution which was filtered and evaporated to dryness in vacuo. To the residue was added 500 ml of anhydrous methanol and a sufficient amount of THF to completely dissolve the residue. An ice bath was added and to the cooled solution was added 4.50 g of sodium hydroxide in 150 ml of methanol. After stirring at room temperature for 24 hr water was added to quench the reaction. After removal of the methanol in vacuo the amine was extracted with chloroform and dried over magnesium sulfate. After filtration and removal of the solvent in vacuo a crude oil was obtained. Addition of the oil to ethyl ether saturated with anhydrous hydrogen chloride gas gave 1.64 g (48.3%) of the amine hydrochloride mp 188-189° (recrystallized from ethyl ether-ethanol). IR free base (NaCl, neat) 3310 cm⁻¹ very weak N-H, 1580 cm⁻¹ N-H. Hydrochloride salt (KBr) 2080-3320 cm⁻¹ very broad. NMR free base (CDCl₃) δ 0.98 (t, J=7 Hz, 2H, NCH₂CH₃), 1.67 (s, 1H, NH, removed with D₂O), 2.42 (q, J=7 Hz, 2H, NCH₂CH₃), 2.80 (d, J=7 Hz, 2H, benzylic), 3.75 (s, 6H, methoxy), 3.75 (t, J=7 Hz, 1H, methine), 3.81 (s, 3H, methoxy), 5.13 (s, 4H, -CH₂O-), 6.27 (s, 2H, aromatic), 6.75-7.60 (m, 13H, aromatic).

Anal. calcd. for C₃₃H₃₈NO₅Cl: C, 70.24; H, 6.80; N, 2.48. Found: C, 70.02; H, 6.69; N, 2.46.

Method B - In a 250 ml round bottom flask was refluxed 0.90 g (1.66 mmol) of N-acetyl-1-(3,4-dibenzylxylophenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine (96) dissolved in 100 ml of THF
and 15 ml of 0.9 M diborane. After 2 hr the solution was cooled and ethyl ether saturated with anhydrous hydrogen chloride gas was slowly added to the solution. The solution was then made basic with 10% aqueous sodium hydroxide solution and extracted with chloroform. The chloroform solution was then dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was dissolved in ethyl ether and added to 200 ml of ethyl ether saturated with anhydrous hydrogen chloride gas. After recrystallization from ethyl ether-methanol 500 mg (53.4%) of the hydrochloride salt, mp 188-189° was obtained.

*N*-Isopropyl-1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (91c). To a 250 ml 3-necked flask equipped with a magnetic stirrer and under an argon atmosphere was added 1.00 g (2.01 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) dissolved in 150 ml of benzene dried over sodium wire. After cooling the solution in an ice bath 10.0 ml of anhydrous isopropylamine was added followed by 0.35 g of titanium tetrachloride. After stirring at room temperature for four days the solution was filtered and the solvent was removed in vacuo. The crude Schiff-base obtained (IR, NaCl, neat, 1625 cm⁻¹) was dissolved in 150 ml of anhydrous THF and transferred to a 250 ml 2-necked flask under argon. After the addition of 10.0 ml of 0.9 M diborane the mixture was
refluxed for 10 hr. After cooling 25 ml of 10% aqueous sodium hydroxide solution was added and the mixture was further refluxed for 10 hr. After cooling the product was extracted with ethyl ether followed by a second extraction with chloroform. The combined organic layers were dried over magnesium sulfate, filtered, and the solvents were removed in vacuo. The residue was dissolved in ethyl ether and converted to the hydrochloride salt upon the addition of ethyl ether saturated with anhydrous hydrogen chloride gas. Upon the slow evaporation of the ethyl ether solution 500 mg (43.1%) of the hydrochloride salt mp 163.5-165°C (recrystallized from methanol-ethyl ether) was obtained. IR free base (NaCl, neat) 3425 cm⁻¹ broad N-H, 1600 cm⁻¹ N-H. Hydrochloride salt (KBr) 3450, 2950, 2800, 2690 cm⁻¹ all very broad indicative of hydrochloride salt. NMR free base (CDCl₃) δ 0.9 (d, J=6 Hz, 6H, -CH(CH₃)₂), 1.53 (s, 1H, N-H), 2.51 (q, J=6 Hz, 1H, -CH(CH₃)₂), 2.74 (d, J=7 Hz, 2H, benzyl), 3.78-4.0 (m, 10H, methoxy and methine), 5.12 (s, 4H, -CH₂O-), 6.23 (s, 2H, aromatic), 6.62-7.0 (m, 3H, aromatic), 7.20-7.60 (m, 10H, aromatic).

Anal. calcd. for C₃₄H₄₀O₅NCl: C, 70.64; H, 6.97; N, 2.42. Found: C, 70.67; H, 7.05; N, 2.35.

N-Methyl-1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (49). A solution containing 150 mg (0.27 mmol) of N-methyl-1-(3,4-dibenzoyloxyphenyl)-2-
(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (91a) 25 mg of 10% palladium on carbon, and 100 ml of anhydrous ethanol were hydrogenated for 8 hr at 40 psi. After the addition of several drops of ethyl ether saturated with anhydrous hydrogen chloride gas, the solution was filtered through two sheets of filter paper and then concentrated in vacuo to a volume of ca 5 ml. The solution was filtered through a cotton plug, ethyl ether was added until the solution became cloudy, and the product was allowed to crystallize in a saturated ethyl ether chamber. Upon filtration in a glove bag under argon 80 mg (80.0%) of crystalline product mp 183-189° was obtained. The product gave a positive ferric chloride test. IR hydrochloride salt (KBr) 3125, 2950, 2725, 2440 cm⁻¹ very broad indicative of amine hydrochloride. Mass Spectrum CI (isobutane) m/e 334, 303; EI m/e 302, 287. NMR (CD₃OD, 90 MHz) δ 2.47 (s, 3H, N-CH₃), 2.86-3.43 (m, 2H, methylene), 3.61 (s, 3H, methoxy), 3.66 (s, 6H, methoxy), 4.02-4.29 (m, 1H, methine), 6.35 (s, 2H, aromatic), 6.56-6.98 (m, 3H, aromatic).

Anal. calcd. for C₁₈H₂₄O₅NCl: C, 58.46; H, 6.54; N, 3.79. Found: C, 58.26; 6.64; 3.65.

A triacetylated derivative 97 was prepared by stirring 60 mg (0.16 mmol) of the catecholamine 49 overnight with a solution containing 5 ml of pyridine. After evaporation in vacuo 10% aqueous hydrochloric acid solution was added and the solution was stirred for 1 hr. The product was then
extracted with chloroform, washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate, filtered, and evaporated in vacuo to give an oil. IR (NaCl, neat) 1770 cm$^{-1}$ ester carbonyl, 1640 cm$^{-1}$ amide carbonyl.

NMR (DMSO-d$_6$, 345°K, 90 MHz)  $\delta$ 1.70 (s, 3H, NAc), 2.06 (s, 6H, OAc), 2.47 (s, 3H, N-CH$_3$), 2.74-2.90 (m, 3H, methylene and methine), 3.35 (s, 3H, methoxy), 3.42 (s, 6H, methoxy), 6.00 (s, 2H, aromatic), 6.65 (s, 3H, aromatic).

**N-Ethyl-1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (47).** A solution containing 300 mg (0.53 mmol) of N-ethyl-1-(3,4-dibenzylxyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (91b) in 50 ml of methanol and 150 ml of ethanol and 30 mg of 10% palladium on carbon catalyst was hydrogenated for 5 hr. Anhydrous hydrogen chloride gas was bubbled through the solution followed by slow gravity filtration through filter paper under an argon atmosphere. The solution was reduced to ca. 2 ml and placed in a saturated ethyl ether chamber. After slow crystallization 50 mg of product mp 182-184° was obtained. The material gave a positive ferric chloride test. Upon contact with air the material became beige colored and after several minutes became purple. Upon heating to 40° for a prolonged period the material became grayish brown and decomposed. Mass spectrum CI (isobutane) m/e 348, 303; EI 303, 302, 288, 287.
Anal. calcd. for C₁₉H₂₆NO₅Cl: H, 59.43; H, 6.83; N, 3.65.

Found: C, 59.17; H, 6.73; N, 3.53.

N-Isopropyl-1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (50). A solution containing 100 mg (0.17 mmol) of N-isopropyl-1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (91c), 25 mg of 10% palladium on charcoal catalyst, and 100 ml of anhydrous ethanol was hydrogenated for 10 hr at 40 psi. After the addition of several drops of ethyl ether saturated with anhydrous hydrogen chloride gas, the solution was filtered through two filter papers and concentrated in vacuo to a volume of ca 5 ml. The solution was filtered through a cotton plug and ca 70 ml of ether was added. The product was then allowed to crystallize in a chamber saturated with ethyl ether. Upon filtration in a glove bag under argon 61 mg of the salt (88.8%) was obtained as stars mp 171.5-172.5°. The product gave a positive ferric chloride test. IR (KBr) 3600-2200 cm⁻¹ very broad with peaks at 3275, 3125, 2975, 2825, 2700, 2450 cm⁻¹ indicative of catecholamine hydrochloride. Mass Spectrum EI m/e 303, 302, 288, 287.

Anal. calcd. for C₂₀H₂₈O₅NCl: C, 60.37; H, 7.09; N, 3.52. Found: C, 60.16; H, 7.11; N, 3.53.
N-Methyl-1-(3,4-dibenzylxoyphenyl)-2-phenethylamine hydrochloride (93a). To a 500 ml 3-necked flask equipped with a magnetic stirrer and under an argon atmosphere was added 2.00 g (4.90 mmol) of 1-(3,4-dibenzylxoyphenyl)-2-phenyl-ethanone (76b) dissolved in 200 ml of anhydrous benzene. After cooling the solution with an ice bath 0.80 g of titanium tetrachloride was added followed by bubbling anhydrous methylamine through the solution for 15 min. The solution changed from reddish-brown to rose-orange. After 72 hr the solution was filtered and the solvent was removed in vacuo. The crude imine obtained as an oil (IR NaCl, neat 1635 cm⁻¹) was dissolved in 150 ml of THF and transferred to a 2-necked 250 ml flask. After the addition of 25 ml of 0.9 M diborane the mixture was refluxed under argon for 10 hr. After cooling 25 ml of 10% aqueous potassium hydroxide solution was added to the reaction mixture and the solution was refluxed an additional 10 hr. After cooling the product was extracted with ethyl ether and chloroform and the combined extracts were dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was dissolved in ca 5 ml of ethanol and ethyl ether saturated with anhydrous hydrogen chloride gas was added with stirring. Upon cooling for 5 days at 4° 0.90 g (40.0%) of amine hydrochloride mp 115-117° was obtained. IR free base (NaCl, neat) 3325 cm⁻¹ N-H; hydrochloride salt (KBr) 3120-2220 cm⁻¹ broad indicative of amine hydrochloride. NMR free base (CDCl₃) δ
2.13 (s, 1H, N-H exchangeable with D$_2$O), 2.18 (s, 3H, N-CH$_3$), 2.86 (d, J=7 Hz, 2H, methylene), 3.63 (t, J=7 Hz, methine), 5.08 (s, 4H, -CH$_2$O-), 6.58-7.62 (m, 18H, aromatic).

Anal. calcd. for C$_{29}$H$_{30}$O$_2$NCl: C, 75.72; H, 6.57; N, 3.05. Found: C, 75.54; H, 6.59; N, 3.02.

$\text{N-Ethyl-1-(3,4-dibenzyloxyphenyl)-2-phenethylamine hydrochloride (93b).}$ To a 250 ml 3-necked flask under argon and cooled in an ice bath was added 0.50 g (1.22 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-phenylethanone (76b) dissolved in 100 ml of benzene, 0.15 g of titanium tetrachloride, and 5 ml of anhydrous ethylamine. After stirring at room temperature for 48 hr the solution was filtered and evaporated in vacuo. The residue was redissolved in 100 ml of anhydrous methanol and 1.00 g of sodium borohydride was added. After stirring for 6 hr water was added to the reaction mixture and the methanol was removed in vacuo. The residue was dissolved in chloroform, washed with water, dried over magnesium sulfate, filtered and evaporated in vacuo to yield an oil. The oil was dissolved in ca 5 ml of methanol and ethyl ether saturated with anhydrous hydrogen chloride gas was added to yield 194 mg (39.3%) of the amine hydrochloride mp 133-134$^\circ$. The product was identical with previously synthesized material. The NMR free base (CDCl$_3$) $\delta$ 0.93 (t, J=7 Hz, 3H, -CH$_2$CH$_3$), 1.23 (s, 1H, N-H exchangeable with D$_2$O), 2.36 (q, J=7 Hz, 2H, -CH$_2$CH$_3$), 2.82 (d, J=7
N-Isopropyl-1-(3,4-dibenzyloxyphenyl)-2-phenethylamine hydrochloride (93c).

Method A - To a 250 ml 3-necked flask equipped with a magnetic stirrer and placed under an argon atmosphere was added 1.00 g (2.45 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-phenylethanone (76b) dissolved in 200 ml of benzene dried over sodium wire. After cooling in an ice bath 1.5 g of anhydrous isopropylamine was added followed by 0.30 g of titanium tetrachloride. After stirring at room temperature for 5 days the solution was filtered and the solvent was removed in vacuo. The crude Schiff-base (IR, NaCl neat, 1620 cm⁻¹) was dissolved in 100 ml of anhydrous methanol and cooled in an ice bath. After the addition of 1.00 g of sodium borohydride the solution was stirred at room temperature for 24 hr. Water was then added and the methanol was removed in vacuo. The product was extracted with ethyl ether, dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was redissolved in anhydrous ethyl ether and to the stirred solution was added ethyl ether saturated with anhydrous hydrogen chloride gas. Upon cooling and filtration 560 mg of the amine hydrochloride (46.9%) mp 149.5-151.5° recrystallized from ethanol-ethyl ether was obtained. IR free base (NaCl, neat) 3325 cm⁻¹ N-H; hydrochloride salt
(KBr) 2200-3200 cm⁻¹ very broad indicative of amine hydrochloride. NMR free base (CDCl₃) δ 0.85 (d, J=6 Hz, 6H, CH(CH₃)₂), 1.38 (s, 1H, N-H exchangeable with D₂O), 2.50 (q, J= 6 Hz, 1H, CH(CH₃)₂), 2.83 (d, J=6.5 Hz, 2H, methylene), 3.90 (t, J=6.5 Hz, 1H, methine), 5.12 (s, 4H, -CH₂O-), 6.60-7.62 (m, 18H, aromatic).

Anal. calcd. for C₃₁H₃₄O₂NCl: C, 76.29; H, 7.02; N, 2.87. Found: C, 76.46; H, 7.06; N, 2.93.

Method B - 1.00 g (2.24 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-phenethylamine hydrochloride (89b) was converted to the free base by stirring in 10% aqueous sodium hydroxide and extracting with ethyl ether. The ethereal layer was dried over magnesium sulfate, filtered and evaporated in vacuo to yield an oil. The oil was dissolved in 250 ml of reagent grade acetone and stirred over 3A molecular sieves for 24 hr. The solution was then filtered through a pad of celite and evaporated in vacuo to give a light oil. IR, NaCl neat, 1450 cm⁻¹ Schiff-base. The oil was dissolved in 50 ml of anhydrous methanol and cooled in an ice bath. To this was added 1.00 g of sodium borohydride dissolved in 100 ml of methanol and the solution was stirred for 20 hr. Water was added to the mixture and after in vacuo removal of the methanol solvent the product was extracted with ethyl ether. The ethereal solution was dried over magnesium sulfate, filtered, and evaporated in vacuo. The residue was dissolved in ethyl ether and ethyl ether saturated with anhydrous
hydrogen chloride was added. Upon cooling and filtration
690 mg (63.0%) of the amine hydrochloride mp 149.5-151.5°
was obtained.

N-Methyl-1-(3,4-dihydroxyphenyl)-2-phenethylamine
hydrochloride (52). A solution containing 300 mg (0.65 mmol)
of N-methyl-1-(3,4-dibenzylxoxyphenyl)-2-phenethylamine,
40 mg of 10% palladium on carbon catalyst and 150 ml of
anhydrous ethanol was hydrogenated at 40 psi for 20 hr.
After the addition of 1 ml of ethyl ether saturated with
anhydrous hydrogen chloride the solution was filtered and
concentrated in vacuo to ca 5 ml. The solution was filtered
through a cotton plug, 10 ml of benzene was added, and
the solution was again concentrated in vacuo to ca 3 ml.
Ethyl ether was added and the solution was placed in a
saturated ethyl ether chamber to yield 145 mg (79.5%) of
catecholamine hydrochloride mp 182-185°. IR (KBr) 3420 cm⁻¹
phenolic OH, 3220 cm⁻¹ N-H, 3100-2250 cm⁻¹ broad indicative
of amine hydrochloride.

Anal. calcd. for C₁₅H₁₈O₂NCI:  C, 64.40; H, 6.49; N,
5.01. Found:  C, 64.30; H, 6.68; N, 5.09.

A triacetylated derivative 98 was prepared by stirring
60 mg of the catecholamine (52) overnight with a solution
containing 5 ml of acetic anhydride and 5 ml of pyridine.
After evaporation in vacuo 10% aqueous hydrochloric acid was
added and the solution was stirred 1 hr. The product was
extracted with chloroform, washed with saturated aqueous sodium bicarbonate solution, dried over magnesium sulfate and evaporated in vacuo to yield an oil. IR (NaCl, neat) 1775 cm\(^{-1}\) ester carbonyl, 1650 cm\(^{-1}\) amide carbonyl.

**N-Isopropyl-1-(3,4-dihydroxyphenyl)-2-phenethylamine hydrochloride** (54). A solution containing 310 mg (0.67 mmol) of N-isopropyl-1-(3,4-dibenzyloxyphenyl)-2-phenethylamine hydrochloride (93c), 40 mg of 10% palladium on carbon catalyst and 100 ml of ethanol was hydrogenated at 40 psi for 6 hr. The solution was gravity filtered through 2 filter papers after the addition of several drops of ethyl ether saturated with anhydrous hydrogen chloride gas. The filtrate was concentrated in vacuo to ca 3 ml and filtered through a cotton plug. Ethyl ether was added to the alcoholic solution until it became slightly cloudy and the product was allowed to crystallize in a saturated ethyl ether chamber. The crystals were filtered under argon in a dry bag to give 151 mg (77.4%) of the amine hydrochloride mp 165-166\(^{\circ}\). The product gave a positive ferric chloride test. IR (KBr) 3400 cm\(^{-1}\) phenolic OH, 3125, 2980, 2825, 2610, 2550 cm\(^{-1}\) broad peaks indicative of amine hydrochloride. Mass Spectrum CI (isobutane) m/e 272.

Anal. calcd. for C\(_{17}\)H\(_{22}\)O\(_2\)NCl: C, 66.33; H, 7.20; N, 4.55. Found: C, 66.27; H, 7.15; N, 4.55.
1-(3,4-Dibenzyl-oxyphenyl)-1-(carbonylamino)-2-(3,4,5-trimethoxyphenyl)ethane (94). To a 100 ml round bottom flask cooled in an ice-salt bath was added 1.00 g (1.89 mmol) of 2-(3,4,5-trimethoxybenzyl)-3,4-dibenzyl-oxyphenylacetic acid (73) and 5 ml of water. Enough acetone was added to completely dissolve the acid followed by 1.00 g of triethylamine in 20 ml of acetone and 1.15 g of ethyl chloroformate. After stirring for 30 min 1.00 g of sodium azide dissolved in 10 ml of water was added and stirring was continued for 30 min. The azide was extracted with chloroform, dried over magnesium sulfate, and filtered. After removal of solvent 50 ml of benzene was added and the mixture was heated for 15 min on a steam bath. After in vacuo removal of solvent crude isocyanate 94 was obtained. IR (NaCl, neat) 2270 cm\(^{-1}\) N=C=O. NMR (CDCl\(_3\)) \(\delta\) 2.92 (d, \(J=7\) Hz, 2H, methylene), 3.75 (s, 6H, methoxy), 3.82 (s, 3H, methoxy), 4.67 (t, \(J=7\) Hz, 1H, methine), 5.12 (s, 4H, -CH\(_2\)-O-), 6.27 (s, 2H, aromatic), 6.75-6.93 (m, 3H, aromatic), 7.23-7.58 (m, 10H, aromatic).

Methyl-N-[1-(3,4-dibenzyl-oxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethyl]carbamate (95a). The crude isocyanate 94 was converted to the methyl carbamate by adding 75 ml of anhydrous methanol. After stirring for 4 hr the product was filtered to give 0.82 g (78.1\% calculated from acid 73) product mp 149-150\(^\circ\). IR (KBr) 3340 cm\(^{-1}\) N-H, 1685 cm\(^{-1}\).
carbonyl. NMR (CDCl$_3$) $\delta$ 2.90 (d, J=7 Hz, 2H, methylene),
3.58 (s, 3H, methoxy), 3.67 (s, 6H, methoxy), 3.77 (s, 3H,
methoxy), 4.73 (t, J=7 Hz, 1H, methine), 4.93 (s, 1H, NH),
5.05 (s, 2H, -CH$_2$O-), 5.08 (s, 2H, -CH$_2$O-), 6.13 (s, 2H,
aromatic), 7.18-7.50 (m, 13 H, aromatic).

Anal. calcd. for C$_{33}$H$_{35}$O$_6$N: C, 71.06; H, 6.33; N, 2.59.
Found: C, 70.94; H, 6.20; N, 2.59.

3-(3,4-Dibenzyloxyphenyl)-6,7,8-trimethoxy-1,2,3,4-
tetrahydroisoquinoline (99). To a 100 ml round bottom flask
was added 500 mg (0.93 mmol) of 1-(3,4-dibenzyloxyphenyl)-
2-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride (89a),
15 ml of 37% formalin, 10 ml of water, and 15 ml of methanol.
The mixture was refluxed for 3 hr and then allowed to cool.
The product, which crystallized out of the cooled reaction
mixture, was filtered and recrystallized from methanol-
water. This was converted to the free base by stirring the
amine hydrochloride with 10% aqueous sodium hydroxide solu-
tion and ethyl ether. The ethereal layer was dried over
magnesium sulfate, filtered and evaporated in vacuo to yield
330 mg (69.1%) of the free base as a white powder mp 138°,
recrystallized from ethyl ether-hexane. IR (KBr) 3310 cm$^{-1}$
N-H. NMR (CDCl$_3$, 90 MHz) $\delta$ 1.74 (s, 1H, N-H), 2.82 (d, J=6.
Hz, methylene), 3.82 (s, 3H, methoxy), 3.85 (s, 3H, methoxy),
3.89 (s, 3H, methoxy), 3.75-4.40 (m, 3H, methine and methyl-
ene), 5.16 (s, 4H, -CH$_2$O-), 6.40 (s, 1H, aromatic), 6.92 (s,
1H, aromatic), 6.93 (s, 1H, aromatic), 7.08 (s, 1H, aromatic), 7.22-7.55 (m, 10H, aromatic). The free base was converted to the hydrochloride salt mp 225-227° by addition of the free base dissolved in a minimum amount of ethanol to anhydrous ethyl ether saturated with hydrogen chloride gas. Mass spectrum CI (isobutane) m/e 512.

Anal. calcd. for C₃₂H₃₄O₅NCl: C, 70.13; H, 6.25; N, 2.56. Found: C, 70.18; H, 6.17; N, 2.49.

3-(3,4-Dihydroxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (56). A solution containing 100 mg (0.18 mmol) of 3-(3,4-dibenzyloxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline (99) dissolved in 250 ml of ethanol and 30 mg of 10% palladium on carbon was hydrogenated for 6 hr at 40 psi. The product was gravity filtered through filter paper and several drops of ethyl ether saturated with anhydrous hydrogen chloride were added. The mixture was evaporated in vacuo to ca 5 ml, filtered through a cotton plug, and anhydrous ethyl ether was added until the mixture became turbid. The solution was then allowed to crystallize in a saturated ethyl ether chamber to give 50 mg (75%) of the catechol as white plates mp 240-241. The material gave a positive ferric chloride test.

Anal. calcd. for C₁₈H₂₂O₅NCl: C, 58.78; H, 6.03; N, 3.81. Found: C, 58.60; H, 6.11; N, 3.80.

A triacetyl derivative 100 was synthesized by stirring
40 mg (0.07 mmol) of the catechol overnight in a solution containing 5 ml of acetic anhydride and 5 ml of pyridine. After evaporation in vacuo 10% aqueous hydrochloric acid was added and the solution was stirred for 1 hr. The product was then extracted with chloroform, dried over magnesium sulfate, filtered, and evaporated to yield an oil. IR (NaCl, neat) 1775 cm⁻¹ ester carbonyl, 1640 cm⁻¹ amide carbonyl. NMR (CDCl₃) δ 2.22 (s, 9H, OAc and NAc), 2.87-3.25 (m, 2H, methylene), 3.82 (s, 3H, methoxy), 3.83 (s, 3H, methoxy), 3.85 (s, 3H, methoxy), 3.95-5.30 (m, 3H, methine and methylene), 6.08 (s, 1H, aromatic), 6.47 (s, 1H, aromatic), 7.98 (2H, aromatic).

**Attempted Synthesis of 2-(3,4-dibenzoyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)piperidine-1,2-imine (104).**

To a 250 ml 3-necked flask under argon and cooled in an ice bath was added 1.00 g (2.01 mmol) of 1-(3,4-dibenzoyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) dissolved in 200 ml of benzene, 0.80 g of piperidine and 0.21 g of titanium tetrachloride. The resulting black solution was stirred for 72 hr, filtered and evaporated in vacuo to yield a golden oil. IR (NaCl, neat) 1580 cm⁻¹ enamine. To the crude enamine dissolved in 100 ml of anhydrous dimethylformamide was added 0.44 g of 3-bromopropylamine hydrobromide (103) and the mixture was refluxed under argon for 18 hr. Water was added to the cooled solution and the
mixture was extracted with chloroform, dried over magnesium sulfate and evaporated in vacuo to yield an oil. Upon the addition of ethyl ether 0.30 g of ketone 76a was recovered. No evidence for alkylated products was observed by NMR spectroscopy of the remaining residue.

1-(3,4-Dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-cyanobutanone (105). Lithium diisopropylamide was generated in situ in a 250 ml round bottom flask under argon and cooled in an ice bath by adding to 0.43 g of diisopropylamine in 5 ml of THF 2.8 ml of 1.67 M n-butyl lithium. After 15 min 2.00 g (4.01 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) dissolved in 100 ml of THF was added in 90 min. Two hours later 0.40 g of acetonitrile dissolved in 0.2 g of HMPA was added and the mixture was stirred at room temperature overnight. Upon acidification with 10% aqueous hydrochloric acid the product was extracted with ethyl ether and chloroform and the combined solutions were dried over magnesium sulfate, filtered, and evaporated in vacuo. Chromatography of the resulting oil on silica gel with 20% ethyl ether in benzene yielded upon crystallization from ethyl ether-chloroform 1.08 g of a fluffy white solid mp 127-128°. IR (KBr) 2240 cm⁻¹ nitrile, 1665 cm⁻¹ carbonyl. NMR (CDCl₃) δ 2.00-2.60 (m, 4H, methylenes), 3.80 (s, 9H, methoxy), 4.37-4.72 (m, 1H, methine), 5.13 (s, 2H, -CH₂O⁻), 5.18 (s, 2H, -CH₂O⁻). 6.46
1-(3,4-Dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)-
2-(2-cyanoethyl)-4-cyanobutanone (106). To a 250 ml flask
equipped with a magnetic stirrer and containing 1.00 g (2.01
mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone 76a was added 0.13 g of sodium hydride (57% suspension).
After 1 hr was added 0.20 g of acetonitrile dissolved in 2.5 ml of THF and stirring was continued for 1 hr. The reaction was then quenched with water and acidified with 10% aqueous hydrochloric acid. The product was extracted with chloroform, dried over magnesium sulfate, filtered and evaporated in vacuo to yield an oil. Following chromatography on silica gel with chloroform containing 1.5% ethanol 0.77 g (58.0%) of the dialkylated product Rf 0.8 was obtained. Crystallization from chloroform-ethyl ether yielded a white solid mp 83-85°. IR (KBr) 2220 cm\(^{-1}\) nitrile, 1660 cm\(^{-1}\) carbonyl. NMR (CDCl\(_3\)) \(\delta\) 1.58-2.65 (m, 8H, methylenes), 3.77 (s, 6H, methoxy), 3.85 (s, 3H, methoxy), 4.98 (s, 2H, -CH\(_2\)O-), 5.17 (s, 2H, -CH\(_2\)O-), 6.30 (s, 2H, aromatic), 6.67-7.52 (m, 13H, aromatic).

Anal. calcd. for C\(_{37}\)H\(_{36}\)O\(_6\)N\(_2\): C, 73.49; H, 6.00; N, 4.63.
Found: C, 73.44; C, 6.12; N, 4.55.
Methyl-5-(3,4-dibenzyloxyphenyl)-4-(3,4,5-trimethoxyphenyl)-5-oxopentanoate (106). Lithium diisopropylamide was generated in situ in a 250 ml 3-necked round bottom flask under argon and cooled in an ice bath by adding to 0.43 g of diisopropylamine in 5 ml of THF 3.0 ml of 1.67 M n-butyl lithium. After 20 min 2.00 g (4.01 mmol) of l-(3,4-dibenzyl-oxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethanone (76a) dissolved in 100 ml of THF was added in 1 hr. After 2 hr 0.60 g of methyl acrylate dissolved in 0.4 g of HMPA was added and stirring was continued for 4 hr. The reaction mixture was then acidified with 10% aqueous hydrochloric acid, extracted with ethyl ether and chloroform and the combined organic layers were dried over magnesium sulfate. After filtration and evaporation in vacuo the residue was chromatographed on silica gel with 20% ethyl ether-benzene to give 1.74 g (74.3 %) of an oil product Rf 0.6. IR (NaCl, neat) 1735 cm\(^{-1}\) ester carbonyl, 1670 cm\(^{-1}\) ketone carbonyl. NMR (CDCl\(_3\)) \(\delta\) 2.10-2.58 (m, 4H, methylenes), 3.62 (s, 3H, methoxy), 3.78 (s, 6H, methoxy), 4.25-4.63 (m, 1H, methine), 5.12 (s, 4H, -CH O-), 6.47 (s, 2H, aromatic), 6.65-7.70 (m, 13H, aromatic).

Anal. calcd. for C\(_{35}\)H\(_{36}\)O\(_8\): C, 71.90; H, 6.21.

Found: C, 72.16; H, 6.19.
Attempted synthesis of 2-(3,4-dibenzyloxyphenyl)-3-(3,4,5-trimethoxyphenyl)piperidine (112). To a 250 ml flask was added 1.20 g (2.18 mmol) of 1-(3,4-dibenzyloxyphenyl)-2-(3,4,5-trimethoxyphenyl)-4-cyanobutanone (105), 100 ml of methanol and enough THF to dissolve the mixture. After cooling the solution in an ice bath 1.00 g of sodium borohydride dissolved in 50 ml of methanol was added and the solution was stirred at room temperature for 3.5 hr. The solvent was then removed in vacuo and the residue was suspended in water. The product was extracted with chloroform, dried over magnesium sulfate, filtered and the chloroform was removed in vacuo to yield 4-(3,4,5-trimethoxyphenyl)-5-(3,4-dibenzyloxyphenyl)-5-hydroxypentanenitrile as an oil. Upon standing the oil solidified to give a solid mp 126-128°. IR (NaCl, neat) 3490 cm\(^{-1}\) hydroxy, 2250 cm\(^{-1}\) nitrile. NMR (CDCl\(_3\)) \(\delta\) 1.37-2.18 (m, 5H, methylene and OH), 2.50-3.00 (s, 1H, -CH(OH)-CH-Ar), 3.73 (s, 6H, methoxy), 3.75 (s, 3H, methoxy), 4.53 (d, J=7 Hz, 1H, -CH-OH), 4.92-5.13 (m, 4H, -CH\(_2\)O-), 6.25 (s, 2H, aromatic), 6.52-6.92 (m, 3H, aromatic), 7.03-7.47 (m, 10H, aromatic).

The alcohol was dissolved in anhydrous ethyl ether, 2 ml of thionyl chloride was added and the mixture was stirred at room temperature overnight. After removal of solvent and recrystallization from ethyl ether-light petroleum ether 1.04 g (83.6%) of 4-(3,4,5-trimethoxyphenyl)-5-
(3,4-dibenzzyloxyphenyl)-5-chloropentanenitrile mp 142-145°.
IR (KBr) 2240 cm⁻¹ nitrile. NMR (CDCl₃) δ 1.54-2.20 (m, 4H, methylene), 2.94-3.32 (m, 1H, CH(Cl)-CH-Ar), 3.79 (s, 6H, methoxy), 3.84 (s, 3H, methoxy), 4.89 (d, J=8 Hz, 1H, CH-Cl), 5.13 (s, 2H, -CH₂O-), 5.16 (s, 2H, -CH₂O-), 6.28 (s, 2H, aromatic), 6.65-6.94 (m, 3H, aromatic), 7.23-7.59 (m, 10H, aromatic).

To a 2-necked 250 ml flask containing 0.50 g (0.87 mmol) of the chloride dissolved in 100 ml of THF was added 25 ml of 0.9 M diborane. The mixture was refluxed under argon for 22 hr. After cooling 0.1 N aqueous sodium hydroxide was added until the evolution of gas from the reaction mixture ceased. The mixture was then refluxed an additional 22 hr. The product was then extracted with ethyl ether and chloroform and the combined extracts were dried over magnesium sulfate. After filtration and in vacuo removal of the solvents a crude oil was obtained. Chromatography of the resulting oil on silica gel with 10% methanol in chloroform saturated with ammonium chloride yielded as the major fraction 148 mg of an oil Rf 0.47. This oil was dissolved in ethyl ether and 15 mg of oxalic acid dissolved in ethyl ether was added. Upon filtration 103 mg of the oxalate salt mp 74-78° was obtained. A correct elemental analysis was obtained for the oxalate salt:

Anal. calcd. for C₃₆H₃₉O₉N₁: C, 68.67; H, 6.24; N, 2.22.
Found: C, 68.52; H, 6.53; N, 2.17.
Reconversion of the salt to the free base by washing with aqueous base yielded an oil. IR (NaCl, neat) 3300 and 3370 cm$^{-1}$ N-H. NMR (CDCl$_3$) $\delta$ 1.08-1.92 (m, 7H), 2.30-2.92 (m, 5H), 3.63-3.92 (m, 1H), 3.75 (s, 6H, methoxy), 3.78 (s, 3H, methoxy), 4.98 (s, 2H, -CH$_2$O-), 5.05 (s, 2H, -CH$_2$O-), 6.20 (s, 2H, aromatic), 6.37-6.87 (m, 3H, aromatic), 7.12-7.57 (m, 10H, aromatic). Treatment of the oil, Rf 0.47, with acetic acid and pyridine yielded an oil after washing and extraction. IR (NaCl, neat) 3310 and 3380 cm$^{-1}$ N-H. NMR (CDCl$_3$) $\delta$ 0.7-1.62 (m, 8H), 1.87 (s, 3H, NAc), 2.57-2.87 (m, 2H), 2.90-3.42 (m, 2H), 3.70 (s, 6H, methoxy), 3.77 (s, 3H, methoxy), 4.97 (s, 2H, -CH$_2$O-), 5.03 (s, 2H, -CH$_2$O-), 6.18 (s, 2H, aromatic), 6.40-6.85 (m, 3H, aromatic), 7.10-7.42 (m, 10H, aromatic).
B. BIOLOGICAL

Isolated Tracheal Strip Preparation. Guinea pigs of either sex weighing 300-500 g were killed by a sharp blow on the head. The trachea of each animal was isolated and cleaned free of fatty tissue. From each guinea pig two spiral tracheal strips were prepared and mounted in a 12 ml jacketed muscle chamber containing a modified Kreb's solution (composed in mmol: NaCl, 118; KCl, 4.7; MgCl$_2$·6H$_2$O, 0.54; CaCl$_2$·2H$_2$O, 2.5; NaH$_2$PO$_4$, 1.0; NaHCO$_3$, 25; glucose, 11) maintained at 37°C through which a mixture of 95% CO$_2$ was bubbled. Drug-induced effects were recorded on a Grass polygraph (Model 7C) via a force displacement transducer. Strips were allowed to equilibrate for 1-1.5 hr before each experiment under a tension of 1 g. Carbachol (3 X 10$^{-7}$ M) was used to increase the tone of each preparation and cumulative dose-response curves were obtained for each drug. Individual plots of tracheal relaxation, expressed as a percent of the maximum relaxation obtained with 10$^{-5}$ M isoproterenol added at the end of each experiment vs. log molar concentration of each drug, were prepared and the ED$_{50}$ values determined individually. In all biological experiments the ED$_{50}$ values represented the concentration of each agonist required to produce a response equal to one-half of the maximal response in the appropriate system.

Isolated Right Atrial Preparation. Guinea pigs of either sex were killed by a sharp on the head. The atrium
was dissected from extraneous tissue and placed in a 12 ml jacketed muscle bath. The atrium was allowed to equilibrate for a 1 hr period in a modified Kreb's solution maintained at 37°C through which a mixture of 95% O₂-5% CO₂ was bubbled. The increase in atrial rate was recorded on a Grass polygraph (Model 7C) via a force displacement transducer.

In each experiment, the atrium was exposed to a test dose of a drug and the atrial rate recorded during a 3 min period. Individual recordings were made at 1 and 3 min intervals. Cumulative dose-response curves were obtained for each analog. The data were plotted on a log scale and the chronotropic responses expressed in terms of the maximum response obtained in the presence of 10⁻⁵ M isoproterenol added at the end of each experiment. ED₅₀ values were determined from individual plots.

**Isolated Fat Cells.** Epididymal fat tissue obtained from nonfasted male Sprague-Dawley rats weighing 200-250 g was used. Fat cells were isolated by the method of Rodbell after digestion of adipose tissue with crude collagenase (Worthington) in a Krebs bicarbonate buffer containing 3% bovine serum albumin.

Incubation mixtures contained 0.2 ml of fat cell suspension, test drug, and Krebs bicarbonate-albumin solution in a total volume of 2.5 ml. Drugs were tested in the concentration range of 1 X 10⁻⁸ - 3 X 10⁻⁴ M. Flasks were incubated in air at 37°C for 1 hr. All reactions were
terminated by the addition of an equal volume of 10% trichloroacetic acid and the amount of glycerol released was measured by procedures described previously.\textsuperscript{169,170}

In each experiment, a maximal release of glycerol was obtained in the presence of $10^{-6}$ M isoproterenol and this maximal figure was used to calculate the dose-response relationships obtained in the study.

\textbf{Drugs.} All drugs were prepared in normal saline containing 0.05% sodium metabisulfite.
SUMMARY

It has been proposed that the 1-arylmethyl group of trimetoquinol may substitute for the β-hydroxyl group of phenethanolamine in helping to achieve the proper binding of trimetoquinol within the β-receptor. In order to study the biological activity produced by placing the 1-arylmethyl substituent of trimetoquinol in a position corresponding to the position of the β-hydroxyl group of phenethanolamine 4-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline and the corresponding norepinephrine analog 2-(3,4,5-trimethoxyphenyl)-3-(3,4-dihydroxyphenyl)propylamine have been synthesized. When tested in the β-adrenoceptor systems of guinea pig atria and trachea both of these analogs possessed lower pD2 values than the parent compound dl-trimetotoquinol. However, although the 4-substituted analog of trimetoquinol was at least 100-fold less potent than the parent compound in tracheal relaxation it appeared to be a more selective bronchodilator than trimetoquinol since it was inactive in guinea pig atria.

In order to synthesize a more potent and selective bronchodilator than trimetoquinol the effect of cleaving the tetrahydroisoquinoline ring system between the 4-position carbon and the aromatic ring has been studied through the
synthesis of N-ethyl-1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine. Furthermore, in order to study the effect of varying the N-alkyl substituents 1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine and its N-methyl and N-isopropyl analogs were also synthesized. All of the fragmented derivatives possessed an ability to produce tracheal relaxation, chronotropic response, and lipolytic response in the β-adrenoceptor systems of guinea pig trachea and atria and rat epididymal fat cells. None of the analogs, however, exhibited any selectivity for the β-adrenoceptor systems over that observed with trimetoquinol. Of the synthesized analogs N-methyl-1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine was the most potent, being at least 100-fold less active than dl-trimetoquinol in the β-adrenoceptor systems examined.

Similarly N-substituted 1-(3,4-dihydroxyphenyl)phenethylamines were synthesized in order to determine if a similar pattern of biological activity could be observed when the benzyl analog of trimetoquinol, 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, was fragmented. Unlike the trimethoxy series, in this series fragmentation led to compounds which exhibited selective β-adrenergic activity. The N-methyl analog was the most active and selective compound of the series being equally active with 1-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline in tracheal relaxation while being inactive in eliciting a
Finally, in order to gain some insight into the conformational relationship between the two aromatic rings of trimetoquinol 3-(3,4-dihydroxyphenyl)-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline has been synthesized. This cyclized analog of N-methyl-1-(3,4-dihydroxyphenyl)-2-(3,4,5-trimethoxyphenyl)ethylamine in which the two aromatic rings are in an anti-relationship was only weakly active in tracheal relaxation. Moreover, it was inactive in eliciting a chronotropic response in atria or releasing glycerol from fat cells. Also described in the attempted synthesis of cis- and trans-2-(3,4-dihydroxyphenyl)-3-(3,4,5-trimethoxyphenyl)piperidine.

In conclusion, the 4-(3,4,5-trimethoxybenzyl) substituted analog of trimetoquinol appears to be more selective than trimetoquinol for the β-adrenoceptor system of guinea pig trachea versus atria. Further investigation of 4-arylmethyl substituted analogs may lead to bronchodilators which are more potent and selective β₂-agonists than trimetoquinol.
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