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Adejare, Adeboye

PART I. FLUORINATED BENZYLIMIDAZOLINES AS AGENTS FOR PROBING THE ALPHA-ADRENERGIC RECEPTOR. PART II. SYNTHESIS, BETA-ADRENERGIC AND ANTIPLATELET ACTIVITIES OF TRIMETOQUINOL ANALOGS

The Ohio State University

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PART I. FLUORINATED BENZYLIMIDAZOLIDINES AS AGENTS FOR PROBING THE $\alpha$-ADRENERGIC RECEPTOR

PART II. SYNTHESIS, $\beta$-ADRENERGIC AND ANTIPLATELET ACTIVITIES OF TRIMETOQUINOL ANALOGS

DISSERTATION

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

by

Adeboye Adejare, B.S., M.S.

* * * * *

The Ohio State University

1985

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DEDICATION

To Dad, Mom and BB
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ORGANIC-MEDICINAL CHEMISTRY
PUBLICATIONS AND MEETING PRESENTATIONS:


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PART I

FLUORINATED BENZYLIMIDAZOLINES AS AGENTS FOR PROBING THE α-ADRENERGIC RECEPTOR
Documented study of the adrenergic system dates back to 1895 when Oliver and Schaefer\textsuperscript{1} found that extracts of the adrenal gland produced a pressor response and a general stimulant effect on smooth muscle. The active constituent was later isolated, shown to be adrenaline\textsuperscript{1} (epinephrine)\textsuperscript{2} and accepted to be the neurotransmitter (sympathin) at sympathetic neuroeffector junctions for about the next four decades.\textsuperscript{3} It was not recognized that norepinephrine\textsuperscript{2} rather than epinephrine, is the principal transmitter at sympathetic synapses until the 1940s when von Euler\textsuperscript{4,5} was able to demonstrate that the principal catecholamine stored and released in bovine cardiac and nerve tissues is norepinephrine.

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{NHR}
\end{align*}
\]

\[
\begin{align*}
1 & \quad R = \text{CH}_3 \\
2 & \quad R = \text{H}
\end{align*}
\]
There are three major naturally occurring neurotransmitter catecholamines, namely R-(-)norepinephrine, R-(-)epinephrine and dopamine, being found widespread throughout the animal kingdom. In the mammalian nervous system, norepinephrine functions as the transmitter at the peripheral neuroeffector junctions of the sympathetic nervous system (heart, smooth muscle and glands) and dopamine has a peripheral role thus far identified in the renal vasculature and ganglionic transmission. Both norepinephrine and epinephrine are liberated from the adrenal medulla but epinephrine is dominant.

![Chemical structure of dopamine](image)

The relationship of parts of the nervous system is shown in Figure 1. The norepinephrine pathways in the central nervous system (CNS) are diffuse and appear to be concerned with many generalized CNS functions including sleep, emotion, temperature regulation, neuroendocrine functions, appetite control and vasomotor function. The dopamine pathways are more discretely localized and include the nigro-neostriated system which is involved in motor control, hypothalamic-pituitary control and mental function. The
Figure 1: Components of the Nervous System
adrenergic nervous system, which is the branch of the autonomic nervous system in which norepinephrine is the neurotransmitter between the nerve ending and the effector muscle, plays an important role in regulating many physiological functions including blood pressure, heart rate and force, gastrointestinal motility and bronchial tone.\textsuperscript{8,9}

Biosynthesis of norepinephrine\textsuperscript{3} takes place at nerve endings. This biosynthesis, which starts with tyrosine, is shown in Figure 2. Tyrosine, an amino acid, is capable of entering the neuron. From tyrosine, via the intermediate compound dihydroxyphenylalanine (L-dopa), the neurotransmitters dopamine, norepinephrine and epinephrine are biosynthesized in the neuron. Dopamine is the direct precursor of norepinephrine, and epinephrine is formed by the action of phenylethanolamine N-methyltransferase on norepinephrine. Synthesized norepinephrine is stored as adenosine triphosphate (ATP)-protein complex in granules at nerve endings\textsuperscript{10} from where it is released upon stimulation. Epinephrine biosynthesis takes place mainly in the adrenal gland, but some biosynthesis is found in the CNS.

Upon stimulation, norepinephrine is released into the synaptic cleft, a process which is calcium (Ca\textsuperscript{2+}) dependent.\textsuperscript{3,11} Diagram of a synapse is depicted in Figure 3. The distance of the synaptic cleft varies from close junctions on the rat and mouse vas deferens (\approx 200 \, \text{Å}) to
Figure 2: Biosynthesis of Norepinephrine and Epinephrine
Figure 3: Schematic Representation of a Synapse
extremely loose junctions (= 10,000 Å) in some vascular tissues. Such considerations of synapse geometry are important in determining the concentrations of neurotransmitter achieved at the postsynaptic receptors, the rates of onset and offset of responses and the importance of different routes of inactivation of the transmitter. Norepinephrine can diffuse across the synapse and act at its receptor on the effector cell (another neuron or organ such as smooth muscle, cardiac muscle or gland cell). Many biochemical events then follow this binding.

The adrenergic receptor is a membrane bound receptor. Biochemical events following binding of an agonist to this receptor differs between α- and β-adrenergic receptors. In the case of the α-adrenoceptor, the activation leads to changes in cell Ca++ fluxes which apparently result in a rise in cytosolic Ca++. The changes may involve influx of extracellular Ca++ through Ca++ "gates" in the plasma membrane or release of Ca++ from intracellular organelles such as mitochondria. Activation of the β-adrenergic receptor leads to an increase in the activity of adenylase cyclase, an enzyme coupled to this receptor. Adenylate cyclase then converts ATP to cyclic-3',5'-adenosine monophosphate (cAMP) thus leading to an increase in intracellular cAMP. The second messengers Ca++ and cAMP can then lead to a variety
of physiological processes including activating other enzymes.

After non-covalent interaction of norepinephrine with the receptor, norepinephrine can be removed in many ways. It is rapidly and efficiently reabsorbed into the presynaptic neuron and then into its storage sites by a process known as uptake. The greatest quantity of norepinephrine is removed in this way.

A number of uptake mechanisms may exist. Uptake, which has a relatively high stereospecific requirements for the neurotransmitter may involve an active transport system since the neurotransmitter must enter the neuron and storage vesicles against a concentration gradient, 1000:1 or more. This uptake system is saturable, has strict ionic requirements, being virtually completely dependent on the presence of sodium ($Na^+$) and low potassium ($K^+$) in the external medium. It is inhibited by ouabain which inhibits the $Na^+\text{-}K^+$-ATPase (sodium pump) presumably because this uptake system utilizes energy generated by the downhill transport of $Na^+$, the operation of the sodium pump being required to maintain the transmembrane $Na^+$ gradient. This uptake system also is inhibited by cocaine and tricyclic antidepressants such as imipramine. Uptake systems similar to this operates for other neurotransmitters such as 5-hydroxytryptamine, amino acids and sugars.
Structural demands of uptake\textsubscript{1} has been studied.\textsuperscript{3} Apart from selectivity for the (−) isomer of norepinephrine, other broad conclusions on the structural demands have been made. The phenolic hydroxy and α-methyl groups are necessary for good affinity for this uptake site whereas N-alkyl, methoxy instead of phenolic hydroxy and β-hydroxy groups all lead to decrease in affinity. This norepinephrine neuronal uptake system is of enormous importance in the delineation of the structure-activity relationships of sympathomimetic amines and has formed the basis for classification of sympathomimetic amines into direct, indirect and mixed acting agents by Fleckeinstein and Burn.\textsuperscript{12} Direct acting agents act on the receptors and have activity that is not affected by inhibitors of uptake\textsubscript{1} and are active regardless of whether or not norepinephrine storage sites have been depleted by agents such as reserpine\textsuperscript{6}. Indirect acting agents serve to displace norepinephrine from nerve terminal storage sites and thus have activity that is affected by reserpine. Activity of indirect acting amines also is sensitive to inhibitors of the uptake\textsubscript{1} system. Mixed acting amines can share both mechanisms. Examples of these three classes of agents are norepinephrine\textsuperscript{2} (direct), tyramine\textsuperscript{7} (indirect) and ephedrine\textsuperscript{8} (mixed). Uptake\textsubscript{2}, the extraneuronal uptake occurs in cardiac muscle, smooth muscle and glands. It has a lower
affinity for norepinephrine and epinephrine than neuronal uptake, is not stereoselective and is not inhibited by cocaine and desipramine. It operates when higher concentrations of the neurotransmitter or structurally related compounds are present at the receptor. By this process, amines structurally related to norepinephrine may be taken up by the neuron.

Enzymatic inactivation of norepinephrine before and after uptake also plays a significant role in the disposition of norepinephrine. The most important enzymes for the metabolism of norepinephrine are monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT). The reactions involving these two enzymes are illustrated in Equations 1 and 2. MAO is found both intraneuronally and extraneuronally, has a very high concentration in the liver and is responsible for the oxidation of many phenethylamine structures to the corresponding aldehydes. This enzyme is not very specific and is inhibited by pargyline. COMT also is an enzyme that is not very specific, methylating many catechols at the meta position on the phenyl ring and is inhibited by tropolone. It is a widespread cytoplasmic enzyme and substantial amounts are found in liver, kidney and sympathetically innervated tissues. While neither MAO nor COMT may represent the primary mode of inactivation of catecholamines released
\[
\text{NH} - \text{CH}_2 - \text{N} - \text{CH}_2 - \text{C} = \text{CH}
\]

\[
\text{O} \quad \text{OH}
\]

\[
\text{HO} \quad \text{HO}
\]

\[
3
\]

\[
\text{NH}_{\text{H}_2}
\]

\[
\text{HO} \quad \text{HO}
\]

\[
\text{MAO} \quad \text{MAO}
\]

\[
\text{HO} \quad \text{HO}
\]

\[
11
\]

\[
\text{NH}_{\text{H}_2}
\]

\[
\text{CH}_3 \quad \text{O}
\]

\[
\text{OH}
\]

\[
\text{CH}_3 \quad \text{O}
\]

\[
\text{NH}_2
\]

\[
12
\]

\[
\text{HO} \quad \text{HO}
\]

\[
\text{COMT} \quad \text{COMT}
\]

\[
\text{CH}_3 \quad \text{O}
\]

\[
\text{NH}_2
\]

\[
12
\]
at nerve terminals (primary mode of inactivation is by the uptake processes discussed above), MAO serves to inactivate neuronal catecholamines not protected by intracellular storage and COMT serves to inactivate extraneuronal catecholamines.

The importance of \( \alpha \)-adrenergic receptors has led this area of research to be a very active one.\(^{13-17}\) Timmermans and van Zweiten in their review\(^{14}\) have discussed the uses and potential uses of drugs that act on \( \alpha \)-adrenoceptors. Apart from the well-known applications of \( \alpha \)-adrenoceptor agonists as nasal decongestants (e.g. naphazoline\(^{13}\), oxymetazoline\(^{14}\), xylometazoline\(^{15}\)) and as additives to local anesthetics, centrally acting antihypertensive agents like clonidine\(^{16}\) and \( \alpha \)-methyl-DOPA\(^{17}\) exert their pharmacological actions by virtue of their interference with \( \alpha \)-adrenoceptors in the central nervous system.\(^{14}\) Stimulation of \( \alpha_2 \)-adrenoceptors in the eye lowers intraocular pressure thus raising the possibility of the use of \( \alpha \)-adrenoceptor agonists for treatment of glaucoma. The inhibitory effects of \( \alpha_2 \)-adrenoceptor agonists on intestinal motility suggests a novel therapeutic approach for the treatment of excessive gastrointestinal motility and diarrhea. Recent investigations have suggested that at least part of the vasodilator activity of calcium slow channel
blockers may involve an interaction with $\alpha$-adrenoceptors. Possible use of $\alpha_2$-antagonists as antidepressants also has been described by Chapleo and coworkers.

The $\alpha$-adrenergic receptor has been subdivided into two groups namely $\alpha_1$ and $\alpha_2$. The subdivision was first based on the pharmacological location of these receptors; $\alpha_1$ being postsynaptic and $\alpha_2$ being presynaptic. However, $\alpha_2$-receptors have also been found on platelets, providing an example of nonpresynaptic $\alpha_2$-receptor. DeMarinis and coworkers recently reported the synthesis of benzazepine, a selective $\alpha_2$ antagonist. It was then coupled to sepharose to form an affinity adsorbent. This gel was shown to adsorb solubilized $\alpha_2$-receptors from human platelet membranes. The $\alpha$-receptors found in rat aorta were a mixed population of $\alpha_1$- and $\alpha_2$-receptors located postsynaptically. Postsynaptic $\alpha_2$-adrenoceptors have also been demonstrated to occur in vascular smooth muscle, pancreatic islets, melanocytes, adipocytes, central nervous system, kidney and eye. All organs subject to neuronal control by the sympathetic nervous system contain postsynaptic $\alpha_1$-adrenoceptors. Presynaptic $\alpha_2$-adrenoceptors have been demonstrated to occur at almost all norepinephrine axons where postsynaptic $\alpha_1$-adrenoceptors were known to exist.
The current classification of $\alpha$-adrenergic receptors is based on the activity of certain agonists and antagonists. One of the parameters used for this demarcation is the isomeric ratio. The isomeric ratio is defined as the potency ratio obtained by dividing the $ED_{50}$ of the less active enantiomer by the $ED_{50}$ of the more potent enantiomer. This ratio is relatively constant for any given pair of enantiomers interacting with a receptor. The receptor may be in different tissues thus this ratio may be used to characterize receptor types and subtypes. The stereochemical requirements for activation and blockade of $\alpha_1$- and $\alpha_2$-adrenoceptors have been described. Based on the observation that larger isomeric activity ratios for the enantiomers of norepinephrine are obtained at $\alpha_2$-adrenoceptors relative to $\alpha_1$-adrenoceptors, it has been proposed that the stereochemical demands made by $\alpha_2$-adrenoceptors for optically active phenethylamines are more stringent than those made by $\alpha_1$-adrenoceptors. This stereochemical preference also has been demonstrated in the case of $\alpha$-methyldopamine. Assymetry at the $\alpha$-carbon atom of this phenethylamine is a major factor affecting the $\alpha$-adrenoceptor subtype selectivity for this class of agonist, the $\alpha_2$ being more able to accommodate the $\alpha$-methyl group of phenethylamines. In the case of $\alpha$-methyl norepinephrine, of the four
possible stereoisomers, the activity at both $\alpha$-adrenoceptor subtypes resides mainly in the $1R,2S$-(−)-erythro form. The isomeric activity ratio for the enantiomeric $1R,2S$-(−)-erythro and $1S,2R$-(+)-erythro pair is approximately 60 fold at $\alpha_1$-adrenoceptors and 530 at $\alpha_2$-adrenoceptors.\textsuperscript{16,23} The fact that $1R,2S$-(−)-$\alpha$-methylnorepinephrine is also more potent than $R$-(−) norepinephrine has led to the suggestion of a four point interaction (i.e. catechol, $\beta$-hydroxyl, amino and $\alpha$-methyl groups) at the $\alpha_2$-receptor.\textsuperscript{23,25} Studies with conformationally restricted phenethylamines indicate that phenethylamines interact with $\alpha_1$- and $\alpha_2$-adrenoceptors in the trans-extended conformation, which also is the predominant conformation in solution and in the solid state.\textsuperscript{16,17,26,27}

![Chemical Structure](image)

19 $R = H$

20 $R = OH$

Activity of other compounds for the $\alpha$-adrenoceptor has been described.\textsuperscript{14} Agonists selective for $\alpha_2$-adrenoceptor include guanabenz \textsuperscript{21} and those selective for $\alpha_1$ include methoxamine \textsuperscript{22} and cirazoline \textsuperscript{23}. Agonists without much
selectivity for either of the \(\alpha\)-subtypes include tramazoline
\(^{24}\), norepinephrine \(^{2}\) and epinephrine \(^{1}\). Differences in \(\alpha_1\)-
and \(\alpha_2\)-antagonist activities of yohimbine isomers namely
corynanthine \(^{25}\), yohimbine \(^{26}\) and rauwolscine \(^{27}\) have been
reported. \(^{14,16,28,29}\) Rauwolscine \(^{27}\) and yohimbine \(^{26}\) selec-
tively block \(\alpha_2\)-adrenoceptors whereas corynanthine \(^{25}\) is se-
lective for blockade of \(\alpha_1\)-adrenoceptor. Since these com-
pounds are diastereomers and consequently possess similar
physiochemical properties, they have become very useful
tools in identifying and subclassifying \(\alpha\)-adrenergic recep-
tors. Other antagonists which are selective for
\(\alpha_1\)-adrenergic receptor include prazosin \(^{28}\) (highest activity
and selectivity) \(^{14}\) whereas those selective for \(\alpha_2\) include
RX 781094 \(^{29}\). Phentolamine \(^{30}\), piperoxan \(^{31}\), tolazoline \(^{32}\)
and phenoxybenzamine \(^{33}\) are examples of non selective
\(\alpha\)-adrenergic blockers.

Physiological and/or functional differences between \(\alpha_1\)-
and \(\alpha_2\)-adrenergic receptors have been addressed. The exci-
tation of postsynaptic adrenergic receptor leads to smooth
muscle constriction whereas excitation of the presynaptic
adrenergic receptor leads to inhibition of norepinephrine
release. The latter process might represent a negative
feedback mechanism which can be activated by norepinephrine
in the synapse.
A better understanding of receptors, their subtypes and the development of selective agonists and antagonists have led to the introduction of clinically relevant and interesting new drugs. Such a development has for instance been observed for \( \beta \)-adrenergic, cholinergic, histaminergic, dopaminergic and serotoninergic receptors. For this reason, it can be anticipated that new drugs based upon interaction with various subtypes of the \( \alpha \)-adrenoceptors shall be developed in the forthcoming years.

Studies on ring-fluorinated aromatic compounds especially catechols and catechol derivatives form a subject of current interest. An important finding by Kirk and co-workers is the effect fluorine substitution has on the biological activity of norepinephrine. It was shown that a fluorine substituent on the 2, 5 or 6 position dramatically affects the activity on adrenergic receptors. Specifically, using guinea pig aorta (\( \alpha \)), atria (\( \beta \)) and ileum (\( \beta \)), it was shown that fluorine substitution on positions 2 and 6 led to selectivity for \( \beta \)- and \( \alpha \)-adrenergic receptors respectively while maintaining the same level of potency and intrinsic activity. Fluorine substitution at position 5, while not displaying the same type of selectivity for \( \alpha \) or \( \beta \) was slightly more potent than the parent compound norepinephrine. Other pharmacological evaluations carried out
included displacement of α- and β-specific ligands from rat cerebral cortical membranes and were consistent with the observations from the guinea pig systems. Selectivities observed were first ascribed to increase in acidity of the phenolic hydroxy groups and perturbation of the physiochemical properties of the aromatic ring of norepinephrine. Later, selectivities observed with the 2 and 6 norepinephrine isomers were ascribed to rotamer stabilization through hydrogen bonding with the benzylic hydroxy group. Hadzi and coworkers have challenged this latter theory. They calculated the conformational energies for 2- and 6-fluoronorepinephrine isomers, showed the F...HO interaction to be minimal and explained the selectivity of the isomers on the basis of electrostatic effects of the fluorine substituent.

Synthetic entry into these fluorinated compounds involves introduction of fluorine to the phenyl ring via Schiemann reaction and this makes them unattractive synthetic targets. Not only is the overall yield for this procedure low, it involves ring nitration, catalytic reduction, diazotization and photochemical decomposition of a diazonium fluoroborate in fluoroboric acid. Ladd and coworkers have described a new reaction which leads to 2-hydroxyfluoroanisole from the commercially available
fluoroanisole. Elaboration of the hydroxyfluoroanisole to give dimethoxy fluorodopamine also was described. Though the Schiemann reaction is a well known reaction, synthesis of fluorinated catecholamines and derivatives as well as extension of current synthetic methods to this area are limited.\textsuperscript{37-43}
Chapter 2

STATEMENT OF PROBLEMS AND OBJECTIVES

The physiological importance of \( \alpha \)-adrenoceptors has led this area of research to be a very active one. Current trend of research in this field is the development of agonist and antagonists which are selective for either of the two subclasses of the \( \alpha \)-adrenoceptor.

Imidazolines and related groups of compounds have emerged to be important for probing the \( \alpha \)-adrenergic receptor. Imidazoline agonists include cirazoline and several 3,4-dihydroxytolazoline derivatives and antagonists include phenolamine, tolazoline and RX 781094. Some of these compounds are selective for \( \alpha_1 \) (cirazoline) whereas some are selective for \( \alpha_2 \) (RX 781094).

Some 3,4-dihydroxybenzylimidazoline derivatives have been synthesized and found to be potent nonselective \( \alpha \)-adrenoceptor agonists. Furthermore, they have been found not to obey the Easson-Stedman hypothesis for the binding of catecholamines to the adrenergic receptor. Thus the relative order of stimulant activity for the imidazolines was deoxy \( 34 = R(-)-35 > S(+)35 \) whereas the
relative order observed for the phenethylamines was 
R-(-)-epinephrine $>$ S-(+)-epinephrine = epinine (deoxyepi-
nephrine). All substitutions thus far on the imidazoline
ring have led to decrease in activity.\textsuperscript{44-46} Opening the im-
idazoline ring to form amidine derivatives also led to a de-
crease in activity.

\[ \text{HO} - \text{Cl}^- \]

\[ \text{R} = \text{H} \text{ (34)} \]
\[ \text{R} = \text{OH} \text{ (35)} \]

Kirk and coworkers\textsuperscript{31} have been able to obtain selectiv-
ity for $\alpha$- or $\beta$-adrenoceptor by substituting fluorine at the
6 and 2 positions of norepinephrine respectively while main-
taining potency comparable with that of the parent compound.
The 5-fluoro isomer, though not selective was more potent
than norepinephrine in some adrenoceptor systems. However,
such dramatic observations did not occur in the case of do-
pamine.\textsuperscript{32}
In the catecholimidazoline class, derivatives of compound 36 with fluorine substituent on the phenyl ring form attractive targets for examining the effects of fluorine substitution on potency and selectivity on the α-adrenergic receptor. The different permutations possible with mono and multiple fluorine substitution are shown as compounds 36 - 41. Compounds 36 - 38 can be useful in establishing the importance of the location of the fluorine. Compound 39 is of interest since the two fluorine groups are placed in
positions reminiscent of the two chlorine groups on clonidine. Compound 40 will be helpful in establishing the relative importance of the acidity of the two hydroxyl groups of the catechol whereas compound 41 will be useful in establishing the effect of substitution of all phenyl hydrogens with fluorine.

The corresponding series of fluorinated derivatives of compound 35 also seem to be very attractive. These analogs can be made and resolved.44 The effects of fluorine substitution on hydrogen bonding and acidity of the catechol hydroxy groups and how these affect potency and selectivity can be evaluated. Optical isomers of compounds 42 and 43 will be very much useful in evaluating the hydrogen bonding effects.

\[ \begin{align*}
\text{OH} & \quad N \\
\text{HO} & \\
\text{HO} &
\end{align*} \]

\[ \begin{align*}
\text{R}^1 & = F, \text{R}^2 = H \\
\text{R}^1 & = H, \text{R}^2 = F
\end{align*} \]

The objective of this investigation was to synthesize catechol imidazolines 36 and 42. These compounds can then be evaluated for intrinsic activity, potency and selectivity.
in the \( \alpha \)-adrenoceptor systems. These two compounds were chosen from the possible fluorocatecholimidazoline pool for many reasons. Compound 36 will help to establish the importance of the catechol hydroxy groups since the fluorine is ortho and meta to them. Secondly, compound 42 can serve to evaluate importance of the \( \alpha \)-hydroxy group since the only difference between compounds 36 and 42 is the \( \alpha \)-hydroxy group. Another reason was that syntheses of these compounds were seen to be possible from two different approaches.
Chapter 3
RESULTS AND DISCUSSION

CHEMISTRY

Synthetic methods for the preparation of the fluorinated benzylimidazolines can be divided into five major areas of discussion. A sixth area of discussion is on a study performed on the lithiation of m-fluoroanisole, the first reaction in the synthetic scheme to the imidazolines. The discussion will be done in the order listed below.

1. Synthesis of 2-fluoro-3,4-dimethoxybenzyl chloride (45)
2. Synthesis of 2-(2'-fluoro-3',4'-dimethoxybenzyl)imidazoline hydrochloride (54)
3. Synthesis of 2-(2'-fluoro-3',4'-dihydroxybenzyl)imidazoline hydrochloride (36)
4. Synthesis of 2-(2'-fluoro-3',4'-dimethoxy-α-hydroxybenzyl)imidazoline hydrochloride (63)
5. Approach to 2-(2'-fluoro-3',4',α-trihydroxybenzyl)imidazoline hydrochloride (42)
6. Lithiation behaviour of m-fluoroanisole
Synthesis of 2-fluoro-3,4-dimethoxybenzylchloride (45)

There are two major approaches to the synthesis of ring fluorinated catecholamines and derivatives. Either of these could be modified to give the halide 45. This benzylic halide can then be converted to the desired benzylimidazolines. One approach to the halide 45 makes use of classical chemistry and involves introduction of fluorine to the phenyl ring via Schiemann reaction.36 Kirk and coworkers have explored this chemistry34 and used it as a synthetic entry to fluorinated norepinephrines,31 dopamines34 and isoproterenols.37 The Kirk group converted 2-nitroveratraldehyde38 to 2-fluoroveratraldehyde 48 using the Schiemann reaction34,31 as shown in Scheme I. In doing this, the Kirk group developed a method for in situ generation and photochemical decomposition of a diazonium fluoroborate.34 This procedure has the advantage of not having to isolate the diazonium fluoroborate unlike the conventional procedure. However, the overall yield for the introduction of fluorine i.e. from aldehyde 44 to fluoroveratraldehyde 48 is low and involves many steps including the low yield photochemical decomposition step. Reduction of fluoroveratraldehyde 48 to give the benzylic alcohol 49 which can be converted to the halide 45 by using thionyl chloride should be possible since these are standard reactions.
SCHEME I

1a

\[
\begin{align*}
\text{CH}_3\text{O} \quad \text{CH}_3\text{O} & \quad \text{NO}_2 \quad \text{CH}_3\text{O} \\
\text{OH} & \quad \text{CH}_3\text{O} \\
\end{align*}
\]

1. \((\text{CH}_3\text{C})_2\text{O}
2. \text{HNO}_3
3. \text{HCl}
4. \text{Me}_2\text{SO}_4

1. \text{H}^+ \quad \text{CH}_3\text{OH}
2. \text{H}_2, \text{Pt}

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{OCH}_3 \\
\text{NH}_2 & \quad \text{OCH}_3 \\
\end{align*}
\]

1. \text{NaNO}_2, \text{HBF}_4
2. \text{HBF}_4, h\nu

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{O} \\
\text{O} & \quad \text{H} \\
\end{align*}
\]

1. \text{NaBH}_4

\[
\begin{align*}
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\text{OCH}_3 & \quad \text{CH}_3\text{O} \\
\text{CH}_3 & \quad \text{CH}_3 \\
\text{F} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{SOCl}_2 & \quad \text{Cl} \\
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{F} & \quad \text{Cl} \\
\text{CH}_3\text{O} & \quad \text{CH}_3\text{O} \\
\end{align*}
\]
$\text{50}$

1. $n$-BuLi
2. $(\text{MeO})_3\text{B}$
3. $\text{H}_2\text{O}_2$

$\text{51}$

$\text{F}$

$\text{CH}_3\text{O}$

$\text{F}$

$\text{HO}$

$\text{CH}_3\text{O}$

$\text{F}$

$\text{CH}_3\text{O}$

$\text{CH}_3\text{O}$

1. $\text{Me}_2\text{SO}_4$
2. $\text{CH}_2\text{O}$, $\text{HCl}$

$\text{45}$
Another approach to the halide \(45\) was described by Ladd and Weinstock\(^3\) and is illustrated in Scheme Ib. This novel approach starts with a commercially available ring-fluorinated reagent, 3-fluoroanisole. Removal of the most acidic proton on 3-fluoroanisole was done with n-butyllithium followed by conversion of this anion to the desired fluorophenol \(51\) by the Hawthorne method.\(^{39}\) This involved trapping the anion generated with trimethylborate and oxidizing the borate ester with hydrogen peroxide to give the fluorophenol. Methylation of the phenol was done to give fluoroveratrole \(52\) which upon chloromethylation using a modified literature procedure\(^{40}\) gave the desired halide \(45\). All the reactions were reported to proceed in high yields, the overall yield from 3-fluoroanisole to the halide \(45\) being 34%. An interesting observation was that haloalkylation on fluoroveratrole \(52\) gave the desired benzylic halide in 95% yield. Though the \(\text{CH}_2\text{-Cl}\) group could have been added either ortho, meta or para to the fluorine due to the directing influence of the methoxy groups, the strong ortho directing influence of fluorine predominated.

Unquestionably, the method of choice to obtain the halide \(45\) was the Ladd and Weinstock method. Not only is the number of steps shorter and the yields higher, it avoids the problematic introduction of fluorine to a phenyl ring.
Further reactions on this halide to give the series of the fluorinated benzylimidazolines desired was seen as being feasible.

The fluorinated benzylic halide 45 was synthesized as illustrated in Scheme 1b. The electron withdrawing effects of fluorine and methoxy groups combined to make the proton at position 2 of 3-fluoroanisole the most acidic proton. This proton was selectively pulled off with n-BuLi and the anion generated was trapped with trimethylborate. Oxidation of the borate ester obtained with 30% hydrogen peroxide gave the crude phenol 51. In a change from the literature procedure, this brown, crude phenol was purified by distillation to give a light yellow liquid before further reactions were carried out. The methylation procedure was modified and conducted in 88% yield. Unlike in literature, resonance due to ortho methoxy group was found to be split by fluorine, with a coupling constant of 0.95 Hz. Although GC and TLC indicated more than one compound was formed by the haloalkylation procedure, the desired fluorinated benzylic halide 45 could easily be obtained in 86% yield after purification by flash chromatography. The other compounds observed are suspected to be monoalkylated and/or dialkylated products. The coupling between fluorine and the benzylic protons of halide 45 was found to be 1.27 Hz though this was not reported by the Ladd group.
Synthesis of 2-(2'-fluoro-3',4'-dimethoxybenzyl)imidazoline hydrochloride (54)

The imidazoline 54 was synthesized as shown in Scheme II. Reaction of the fluorinated benzylic halide 45 with sodium cyanide gave the nitrile 53. Conversion of nitriles to imidazolines via the Pinner reaction has been well described by Bristow and Miller et al. Pinner reaction on the nitrile 53 was followed by conversion of the intermediate iminoacetate to the imidazoline 54 by reaction with ethylenediamine.

Synthesis of 2-(2'-fluoro-3',4'-dihydroxybenzyl)imidazoline hydrochloride (36)

The synthetic scheme leading to the synthesis of the catecholimidazoline 36 is shown in Scheme III. Attempts to obtain this catechol by demethylation of the dimethoxybenzyl imidazoline 54 were first made. Boron tribromide demethylation was attempted at different temperatures between -75°C and RT. HBr and HI demethylations were also attempted. The major problem with these demethylation procedures seems to be hydrolysis of the imidazoline ring. Though the FeCl₃ test may be positive, indicating presence of a catechol in the reaction product, ¹H NMR spectra of such mixtures were never in accordance with what was expected.
SCHEME II

1. EtOH, HCl
2. H₂N NH₂
3. HCl

45

53

54
Several catecholimidazolines have been obtained by performing hydrogenation on protected imidazolines where the protecting groups were benzyl groups. Therefore, synthesis of the fluorinated catecholimidazoline from the dibenzyl precursor was seen as the next line of approach. The key intermediate in this synthesis was the fluorinated dibenzylxylanitrile, therefore efforts were directed at synthesis of this compound.

In the first trial (Scheme IIIb), boron tribromide demethylation of the fluorophenol provided a fluorocatechol which was benzylated to give 2,3-dibenzylxyfluorobenzene. However, chloromethylation to give the benzylic halide was not successful and this synthetic scheme to the nitrile had to be abandoned. The chloromethylation was carried out as in the synthesis of benzyl halide. It involved bubbling HCl gas to a solution of the fluorobenzene and formaldehyde in acetic acid. Failure of this reaction was probably because the conditions were drastic enough to cause debenzylation of fluorobenzene or the desired halide. The phenols and/or catechols formed can then react with formaldehyde thus forming many products. This scheme was thus not pursued any further. Synthesis of the nitrile was then attempted as shown in Scheme IIIc. Again, this scheme was halted by the failure of the
SCHEME III

IIIa

IIIb

1. BBr₃
2. PhCH₂Cl

CH₂O, HCl

AcOH

NaCN
1. BBr₃
2. PhCH₂Cl

1. EtOH, HCl
2. H₂N─NH₂
3. HCl

H₂, Pd/C

IIIId
demethylation and benzylation step. This failure may be due
to BBr₃ bromination of the benzylic hydroxy part of compound
49. Thus multiple products immediately become feasible dur-
ing the benzylation.

Synthesis of the much desired nitrile 58 was achieved
by BBr₃ demethylation of the nitrile 53 to give a catechol
which was then benzylated. Much care must be taken during
this reaction since there are several reactions competing
with the desired one. Aqueous quenching of the boron tri-
bromide reaction mixture seems to be exothermic and should
be cooled. However, in an attempt where cooling was done
with dry ice-acetone (-75°C), very little product was ob-
tained at the end of the reaction. This was probably be-
cause the HBr generated was absorbed into the solution in-
stead of being bubbled out, as less than normal amount of
gas bubbling was seen during this trial. The HBr absorbed
could then lead to hydrolysis of the nitrile group as temp-
erature warmed up. Cooling with ice-water seemed to suf-
fice. Quenching in the presence of base such as NaHCO₃ and/
or acetonitrile to counteract the effects of HBr did not
seem to make much difference. It is imperative that the
solution in which the benzylation is done be dry so as to
prevent hydrolysis at this point also.
Conversion of the nitrile 58 to the imidazoline 60 was done in a similar manner as in the synthesis of imidazoline 54 above. As expected, hydrogenation of the imidazoline 60 gave the target catecholimidazoline 36.

**Synthesis of 2-(2'-fluoro-3',4'dimethoxy-α-hydroxybenzyl) imidazoline hydrochloride (63)**

The key intermediate in this synthesis was the aldehyde 48 which could have been obtained either directly from the Kirk procedure to ring fluorinated phenethylamines 31 (see Scheme I) or by oxidation of benzylic halide 45 obtained through the Ladd procedure 35. Again, consideration of yield, number of steps and procedures favoured the latter method.

Synthesis of the fluorinated benzylimidazoline 63 is shown in Scheme IVa. Oxidation of the halide 45 to the aldehyde 48 was first achieved with the Hass and Bender procedure 50,51 involving sodium, ethanol and 2-nitropropane. The mechanism for this reaction is shown in Scheme IVb. The anion of 2-nitropropane is generated in situ with sodium ethoxide which in turn was generated from sodium and ethanol. The 2-nitropropane anion is capable of resonance such that the negative charge resides on carbon 2 or oxygen. It should be noted that the product desired results from oxygen
SCHEME IV

IVa

\[
\begin{align*}
&\text{CH}_3\text{O} & \text{F} & \text{Cl} \\
&\text{CH}_3\text{O} & & \\
\end{align*}
\]

\[
\xrightarrow{\text{NO}_2, \text{Na}} \quad \text{or} \quad \text{DMSO}
\]

\[
\begin{align*}
&\text{CH}_3\text{O} & \text{F} & \text{O} \\
&\text{CH}_3\text{O} & & \\
\end{align*}
\]

1. \text{Me}_3\text{SiCN}
2. \text{HCl}

\[
\begin{align*}
&\text{CH}_3\text{O} & \text{F} & \text{OH} & \text{CN} \\
&\text{CH}_3\text{O} & & & \\
\end{align*}
\]

1. \text{EtOH}, \text{HCl}
2. \text{H}_2\text{N}-\text{NH}_2
3. \text{HCl}

\[
\begin{align*}
&\text{CH}_3\text{O} & \text{F} & \text{HO} & \text{HN} & \text{NH} \\
&\text{CH}_3\text{O} & & & & \text{Cl}^- \\
\end{align*}
\]

61
62
63
IVb

\[ \text{NO}_2 \xrightarrow{\text{NaOEt}} \text{NO}_2 \xrightarrow{} \text{NO}^+\text{O}^- \]

\[
\begin{array}{c}
\text{CH}_3\text{O} \quad \text{F} \\
\text{CH}_3\text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3\text{O} \quad \text{F} \\
\text{CH}_3\text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3\text{O} \quad \text{F} \\
\text{CH}_3\text{O} \\
\end{array}
\]

\[
\begin{array}{c}
\text{CH}_3\text{O} \quad \text{F} \\
\text{CH}_3\text{O} \\
\end{array}
\]

\[ \text{NOH} + \]

\[ \text{CH}_3\text{O} \quad \text{F} \quad \text{O} \text{H} \]

\[ \text{CH}_3\text{O} \quad \text{F} \]

\[ \text{CH}_3\text{O} \quad \text{F} \]
IVc

\[
\begin{align*}
&\text{CH}_3\text{O} \quad \text{Cl} \\
&\text{CH}_3\text{O} \\
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3\text{O} \\
&\text{CH}_3\text{O} \\
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3\text{O} \\
&\text{CH}_3\text{O} \\
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3\text{O} \\
&\text{CH}_3\text{O} \\
\end{align*}
\]

+ \text{CH}_3\text{SCH}_3

\[
\begin{align*}
\text{NaHCO}_3
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3\text{O} \\
&\text{CH}_3\text{O} \\
\end{align*}
\]

\[
\begin{align*}
&\text{CH}_3\text{O} \\
&\text{CH}_3\text{O} \\
\end{align*}
\]

+ \text{CH}_3\text{SCH}_3
alkylation of the halide 45 to give the intermediate 68 which can then collapse to give the desired aldehyde. A competing reaction is carbon alkylation 50 to give the nitroalkane 69. Though this method of oxidation gave a 49% yield on a small scale, attempt to scale it up resulted in a lower yield. The other two products isolated are suspected to be the intermediate 68 which upon time decomposed to give the desired aldehyde and the product 69 from carbon alkylation. Kornblum oxidation 52,53 on the halide 45 was then attempted. Not only was a much higher yield (84%) obtained, the procedure was simpler since it only involved heating a mixture of the halide, sodium bicarbonate and dimethylsulfoxide for a few hours. It is imperative that the temperature of the solution not be substantially above 100°C since such results in a lower yield. The mechanism for Kornblum or dimethyl sulfoxide oxidation is shown in Scheme IVc. The oxygen on DMSO eventually becomes the aldehyde oxygen and the residue dimethylsulfide is bubbled out as a gas.

Conversion of the aldehyde 48 to the cyanohydrin 61 was done using Gassman and Talley's method 54 involving the use of trimethylsilyl cyanide and aqueous HCl. Conversion of the nitrile (cyanohydrin) 61 to the benzyl imidazoline 63 was done as usual. The relatively low yield observed in this conversion may be due to replacement of the benzylic
hydroxy group with chlorine during the step involving bubbling HCl gas to the nitrile, ethanol and CHCl₃ mixture.

**Approach to 2-(2'-fluoro-3',4',α-trihydroxybenzyl) imidazoline hydrochloride (42)**

This approach is shown in Scheme V. The key intermediate in this synthesis is the aldehyde 70. Conversion of this aldehyde to the benzyl imidazoline 71 followed by hydrogenation to give the desired catecholimidazoline 42 were envisioned to be no problem. The dibenzyl aldehyde 70 was obtained from the dimethoxyaldehyde 48 at a low yield, at best 26%. However, this aldehyde can be accumulated and the appropriate transformations carried out to give the desired catecholimidazoline.

**Lithiation behaviour of m-fluoroanisole**

The reactions of fluoroanisole with phenyllithium at room temperature have been studied. Synthesis of fluoro-veratroles from fluoroanisole also has been described. The latter study is important because it describes a synthetic entry to many ring-fluorinated compounds such as the pharmacologically important phenethylamines. However,
SCHEME V

1. Me₃SiCN, HCl
2. EtOH, HCl
3. H₂N NH₂
4. HCl

H₂ / Pd / C
reproducibility of the transformation of m-fluoroanisole to 2-hydroxy-3-fluoroanisole 51 (Scheme Ib) proved difficult. This lead to a study of this reaction.56

In this study, optimum conditions leading to the generation of the desired phenol 51 or the other product of the reaction were developed. The other product was also identified to be a biphenyl phenol. Scheme VI shows the pathways leading to both products.

When 3-fluoroanisole was treated with an equimolar amount of n-butyllithium at low temperature (-75°C), it forms the anion 72. This anion can be trapped and developed into the phenol 51.35 Once formed, another option available to the anion is collapse to form the benzyne 73. The benzyne can undergo several reactions including reaction with anion 72 to generate a biphenyl anion. The biphenyl anion resulting from attack at the position meta to the methoxy group of the benzyne is expected to be formed as a result of the stabilizing inductive effect of the benzyne methoxy group. Attack at the position ortho to the methoxy group is not favoured since it will lead to the less stable biphenyl anion. In this study, the anion formed was trapped as the borate ester and oxidized to form the phenol 74.35,37 The crude phenol in methylene chloride was passed over decolourizing carbon and purified by flash chromatography to give the biphenyl phenol in 36% yield.
The time between generation of anion 72 and trapping it seems to be the major determining factor as to the ratio of phenols 51 and 74 formed. Trapping at 2h or less leads to high yield of phenol 51 whereas trapping at 5h leads to high yield of phenol 74. High dilution and low temperature are essential for formation of phenol 51 whereas these do not seem to be as critical in the formation of phenol 74. Methylation was used to confirm the structure of biphenyl phenol 74. Biphenyl 77 would have been obtained on methyla-
tating the phenol resulting from ortho attack of anion 72 on the benzyne. In this case, two of the three methoxy groups should be equivalent. The three methoxy groups on biphenyl 76 would all be expected to be different. Methylation was done using dimethyl sulfate (89% yield). Three different methyl resonances were observed on examining the $^1$H NMR spectrum of the product, confirming structure 76 as the product.

BIOLOGY

Preliminary pharmacological data have been obtained on catecholimidazoline 36. These evaluations were done on rabbit ear arteries ($\alpha_1$) and and guinea pig atria ($\alpha_2$) as described by Hieble and Pendleton.57 The results were ex-
tracted from graphical plots and are shown in Table 1. In the case of $\alpha_1$-adrenoceptor, vasoconstriction was measured whereas inhibition of release of $[^3H]$-norepinephrine was measured for the $\alpha_2$-adrenoceptor. The catecholimidazoline was found to be equipotent (nM concentration level) with the non-fluorinated analog on both $\alpha_1$- and $\alpha_2$-adrenergic receptors. Both compounds also showed slight selectivity for the $\alpha_2$-adrenoceptor. They were found to be displaceable to about the same extent by prazosin and rauwolscine, which are $\alpha_1$ and $\alpha_2$ blockers respectively.

Kirk and coworkers found that fluorine substitution on norepinephrine at position 6 increased selectivity for $\alpha$-adrenergic receptor, whereas substitution at position 2 decreased $\alpha$-adrenergic activity. In this study, it was found that fluorine substitution on position 2' of catecho-limidazoline did not lead to a significant loss of $\alpha$-adrenergic activity. This observation becomes interesting in light of the fact that the catecholimidazolines and were also found not to obey the Easson-Stedman hypothesis (Chapter 2). It also makes synthesis and pharmacological evaluation of the 6-fluorocatecholimidazoline as well as the other analogs described in Chapter 2 more desirable.
### TABLE 1

**α-Adrenergic Activity of Catecholimidazolines 34 and 36**

<table>
<thead>
<tr>
<th>Compound</th>
<th>$pD_2^a (\pm S.E.M.)$</th>
<th>$pK_B^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha_1$</td>
<td>$\alpha_2$</td>
</tr>
<tr>
<td>34</td>
<td>7.13 (.08)</td>
<td>7.58 (.08)</td>
</tr>
<tr>
<td>36</td>
<td>7.10 (.18)</td>
<td>7.52 (.04)</td>
</tr>
</tbody>
</table>

---

$$
\begin{align*}
\text{a} & \quad pD_2 = - \log ED_{50} \\
\text{b} & \quad pK_B = - \log K_B \\
\text{where } K_B = & \frac{\text{[Antagonist]}}{\text{Concentration ratio - 1}} \\
\text{Concentration ratio} = & \frac{[ED_{50}] (\text{Agonist alone})}{[ED_{50}] (\text{Agonist + Antagonist})}
\end{align*}
$$

For $\alpha_1$: antagonist prazosin $139 = 3 \times 10^{-8}$

For $\alpha_2$: antagonist rauwolscine $138 = 1 \times 10^{-7}$
Chapter 4
EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. IR spectra were obtained with a Beckman 4230 infrared spectrophotometer and NMR spectral data obtained with a Bruker HX-90E (90 MHz) or Bruker WP-80DS (80 MHz) NMR spectrometer. Mass spectra were obtained with a DuPont 21-491 mass spectrometer. GC analyses were performed using a Hewlett Packard 5710A GC. Elemental analyses were performed by Galbraith Laboratories Inc., Knoxville, TN. Analytical results for elements indicated were within ±0.4% of the theoretical values. Reagent grade acetone used as solvent in some reactions was dried over K₂CO₃. Hexane, ethyl acetate and petroleum ether were distilled before use. Acetonitrile was refluxed over P₂O₅ overnight and then distilled while THF was dried by refluxing over sodium overnight, distilling and then redistilled over sodium and benzophenone (as the deep blue indicator for dryness). Methanol was distilled over magnesium methoxide, generated in situ from magnesium, iodine and methanol. Ethanol was also distilled over
magnesium ethoxide generated in situ from magnesium, iodine and ethanol. Selected NMR spectra are shown in Appendix A.

2-Hydroxy-3-fluoroanisole (51)

![2-Hydroxy-3-fluoroanisole](image)

A solution of 50.00 g (0.396 mol) of m-fluoroanisole in 450 ml of dry THF was cooled in a dry ice-acetone bath under an argon atmosphere, then 145 ml (0.377 mol) of 2.6 M n-butyllithium in hexane was added dropwise over 30 min while stirring. The resultant solution was stirred for 1.5 h at -75°C after which a solution of 43 ml (0.379 mol) of trimethylborate in 450 ml ether was added dropwise over 40 min. The cooling bath was removed and stirring continued for 1.25 h. A solution of 260 ml 10% HCl was added slowly and the stirring continued for 30 min. The layers were separated and the organic layer washed twice with H₂O, dried over MgSO₄ and concentrated to give 69.50 g of white crystalline boronic acid.

The boronic acid was dissolved in 330 ml toluene with warming then 124 ml 30% H₂O₂ was added slowly to the warm
solution, causing a vigorous exothermic reaction. The reac-
tion mixture was refluxed for 45 min, cooled to room temper-
ature and the layers separated. The organic layer was
washed once with H₂O, twice with freshly prepared
10% ferrous ammonium sulfate and again H₂O. The toluene
filtrate was extracted twice with 10% NaOH and the combined
extracts acidified with concentrated HCl while cooling with
ice-water. Two extractions with CH₂Cl₂ followed by drying
over MgSO₄ and concentrating gave 37.70 g (67%) of crude
phenol as a dark liquid. Purification by vacuum distilla-
tion gave 24.50 g (an overall yield of 44%) of a light yel-
low liquid.
bp = 84-85°C at 2.2 mm Hg (lit. bp = 129.5-131°C
at 30 mm Hg)
¹H NMR (CDCl₃):
6.84-6.58 (m, 3H, Ar-H)
5.40 (br s, 1H, Ar-OH)
3.90 (s, 3H, OCH₃)
IR (neat) cm⁻¹: 3510 (br, OH)
3-Fluoroveratrole (52)

A mixture of 13.45 g (94.6 mmol) of purified phenol 51, 130 ml dry acetone, 26.45 g (191.4 mmol) powdered anhydrous K₂CO₃ and 18 ml (190.2 mmol) Me₂SO₄ was stirred and refluxed for 12 h. After cooling to room temperature, the reaction mixture was diluted with H₂O and extracted twice with ether. The ether extracts were combined, washed twice with H₂O and then stirred for 1.5 h with a 10% NH₄OH solution. The layers were separated and the organic layer washed three times with H₂O, dried over MgSO₄ and concentrated without heat to a yellow liquid. Vacuum distillation gave 13.06 g (88%) of a colourless liquid.

bp = 69-70°C at 2.4 mm Hg (lit. 35 bp = 93.5-106°C at 19-24 mm Hg)

Analysis by GC gave a single peak (SP 2100 column, oven T = 150°C, injection port T = 250°C, detection port T = 250°C).

¹H NMR (CDCl₃):

7.09-6.59 (m, 3H, Ar-H)
3.93-3.92 (d, 3H, OCH₃ ortho to F, J₉F = 0.95 Hz)
3.87 (s, 3H, OCH₃ meta to F)
2-Fluoro-3,4-dimethoxybenzylchloride (45)

HCl gas was bubbled into a solution of 11.01 g (70.5 mmol) of 3-fluoroveratrole 52, 11 ml 37% formaldehyde and 30 ml glacial acetic acid. The reaction was monitored by GC and shown to be complete after 4 h. The mixture was poured in H₂O, extracted three times with ether and the ether extracts combined. The ether solution was washed three times with water, dried over MgSO₄ and concentrated to give a white solid. Purification by flash chromatography using 20% ethyl acetate in hexane as eluting solution was followed by crystallization in CH₂Cl₂/hexane to give 12.34 g (86%) of white crystalline fluorobenzylchloride 45. 

mp = 48-49°C (lit. mp = 44.5-47.5°C)

¹H NMR (CDCl₃):

7.15-6.62 (m, 2H, Ar-H)
4.61-4.60 (d, 2H, Ar-CH₂Cl, JHF = 1.27 Hz)
3.94-3.93 (d, 3H, OCH₃ ortho to F, JHF = 0.95 Hz)
3.88 (s, 3H, OCH₃ meta to F)
2-Fluoro-3,4-dimethoxyphenylacetonitrile (53)

![Chemical Structure]

Sodium cyanide, 1.30 g (26.5 mmol) was added to a solution of 4.20 g (20.5 mmol) 2-fluoro-3,4-dimethoxybenzyl chloride 45 in 75 ml DMSO. A mild exotherm was observed and the mixture was stirred for 1.5 h. The reaction mixture was then poured in 200 ml of ice and extracted three times with ether. The ether extracts were combined, washed four times with H₂O, dried over MgSO₄ and purified by flash chromatography using 25% ethyl acetate in hexane as eluting solution. Removal of solvent under vacuum gave 3.49 g (87%) of the nitrile 53 as a white solid which was crystallized from CH₂Cl₂/hexane.

mp = 48-50°C (lit. yellow oil)

¹H NMR (CDCl₃):

7.16-6.64 (m, 2H, Ar-H)
3.93-3.92 (d, 3H, OCH₃ ortho to F, JHF = 0.95 Hz)
3.88 (s, 3H, OCH₃ meta to F)
3.70 (s, 2H, Ar-CH₂CN)

IR (KBr) cm⁻¹: 2250 (C≡N)
Ethyl-2-(2'-fluoro-3',4'-dimethoxyphenyl)iminoacetate hydrochloride (55)

\[
\text{CH}_3\text{O} \quad \text{F} \quad + \quad \text{NH}_2 \quad \text{Cl}^- \quad \text{OEt}
\]

HCl gas was bubbled into the suspension of 1.86 g (9.528 mmol) of nitrile 53 in 0.45 ml (7.67 mmol) EtOH and 8 ml benzene with cooling in an ice bath. The mixture turned light yellow and ca. 0.5 g of HCl was absorbed. The mixture was allowed to stand at room temperature for 45 min and then kept in the refrigerator for 40 h.

The solid material obtained melted upon warming to RT. Filtration over cotton followed by addition of 10 ml ether to the mixture resulted in the crystallization out of 2.11 g (99%) of a white solid iminoacetate 55.

mp = 100-101°C
2-(2'-Fluoro-3',4'-dimethoxybenzyl)imidazoline hydrochloride (54)

To a solution of 0.93 g (3.35 mmol) of the iminooacetate 55 in 6 ml CH₂Cl₂ was added 0.5 ml (7.48 mmol) ethylenediamine dropwisely while stirring and cooling with an ice bath. The mixture was allowed to warm up to RT and stirring continued for another 15 h. To the resulting mixture was added 10 ml CH₂Cl₂ and 20 ml H₂O. The layers were separated and the organic layer washed with 10 ml H₂O and dried over Na₂CO₃. Removal of solvent under vacuum followed by crystallization in CH₂Cl₂/ether gave 407 mg (51%) of the free base of imidazoline 54 as a white crystalline material. mp = 106-108°C

HCl salt of 230 mg (0.97 mmol) was made. Crystallization in CHCl₃/ether gave 200 mg (75%) of white crystalline imidazoline 54.

mp = 176-177°C

¹H NMR (CDCl₃):

10.29 (s, 2H, NH)

7.38-6.62 (m, 2H, Ar-H)

4.07 (s, 2H, Ar-CH₂)
3.93 (s, 4H, NCH₂CH₂N)
3.87 (s, 3H, Ar-OCH₃ ortho to F)
3.83 (s, 3H, Ar-OCH₃ meta to F)

IR (KBr) cm⁻¹: 3410 (NH), 3060, 1620 (C=N)

MS: 238 (M⁺ - HCl), 207 (base), 169

Analysis for C₁₂H₁₆N₂O₂FCI
Calculated: C, 52.46; H, 5.87; N, 10.20; F, 6.92;
found: C, 52.51; H, 5.93; N, 10.05; F, 6.83.

2,3-Dibenzylxoxyfluorobenzene (56)

To a solution of 5.20 g (36.6 mmol) of the phenol 5₁ in 100 ml CH₂Cl₂ under argon was added 100 ml (100 mmol) 1 M BBr₃ in CH₂Cl₂ dropwise while cooling with dry ice/acetone and stirring. The mixture was stirred at room temperature for 24 h. It was then cooled with ice-water, quenched with H₂O and the CHCl₃ removed under vacuum. Extraction of the aqueous residue four times with ether followed. The combined ether extracts was extracted four times with 2N NaOH and combined. The alkaline extract was
neutralized with 10% HCl and extracted three times with ether. The ether extracts were combined, dried over Na$_2$SO$_4$ and concentrated to give the crude catechol as a dark liquid in a quantitative yield.

To 1.00 g (7.81 mmol) of the catechol in 10 ml absolute ethanol was added 2.00 g K$_2$CO$_3$, 2.1 ml (18.2 mmol) benzyl chloride and 60 mg NaI. After refluxing for 7 h, the mixture was cooled and the ethanol removed under pressure. Water was added to the residue, extracted three times with CHCl$_3$, dried over MgSO$_4$ and purified by flash chromatography using 10% ethyl acetate in hexane as eluting solution to give 1.5 g (62%) of the dibenzyloxyfluorobenzene 56 as a light yellow oil.

$^1$H NMR (CDCl$_3$):

- 7.50-7.30 (m, 10H, Ar-H)
- 6.97-6.60 (m, 3H, Ar-H)
- 5.10 (s, 4H, Ar-CH$_2$)

MS: 308 (M$^+$), 91 (base)

Analysis for C$_{20}$H$_{17}$O$_2$F

Calculated: C, 77.91; H, 5.56; F, 6.16;

found: C, 77.61; H, 5.81; F, 6.36.
2-Fluoro-3,4-dimethoxybenzyl alcohol (49)

A mixture of 1.25 g (6.11 mmol) of benzylic halide 45, 20 ml toluene and 20 ml 10% NaOH was refluxed for 20 h after which TLC showed the reaction to be complete. Developing solution for the TLC was 20% ethyl acetate in hexane. The reaction mixture was separated and the aqueous layer extracted twice with CH$_2$Cl$_2$. The toluene layer was concentrated, redissolved in CH$_2$Cl$_2$ and the CH$_2$Cl$_2$ portions combined and washed three times with H$_2$O. Drying over MgSO$_4$ and removal of CH$_2$Cl$_2$ under vacuum gave 1.02 g (90%) of the alcohol 49 as a light yellow oil.

$^1$H NMR (CDCl$_3$):

7.17-6.57 (m, 2H, Ar-H)
4.64 (s, 2H, Ar-CH$_2$)
3.89-3.88 (d, 3H, OCH$_3$ ortho to F, $J_{HF} = 0.98$ Hz)
3.83 (s, 3H, OCH$_3$ meta to F)
1.97 (br s, 1H, OH)

IR (neat) cm$^{-1}$: 3400 (br, OH)

MS: 186 (M$^+$), 59 (base)
2-Fluoro-3,4-dibenzylxoxyphenyl acetonitrile (58)

\[
\begin{align*}
\text{PhCH}_2\text{O} & \quad \text{F} \\
\text{PhCH}_2\text{O} & \quad \text{CN}
\end{align*}
\]

Dropwise addition of 10 ml (10 mmol) 1 M BBr\textsubscript{3} in CH\textsubscript{2}Cl\textsubscript{2} to a solution of 671 mg (3.44 mmol) of benzyl nitrile 5\textsubscript{3} in 1.5 ml CH\textsubscript{2}Cl\textsubscript{2} under argon was done at RT while stirring. The mixture became warm and was allowed to stir at RT for 20 h. After this, it was cooled down with dry ice-water and quenched with 20 ml cold H\textsubscript{2}O. The mixture was extracted three times with ether. The ether extracts were combined and concentrated.

FeCl\textsubscript{3} test for catechols: positive

To the residue obtained from the ether layer was added 20 ml THF, 1.20 g K\textsubscript{2}CO\textsubscript{3}, 50 mg NaI and 1.2 ml (10.43 mmol) benzyl chloride and the mixture refluxed overnight. The FeCl\textsubscript{3} test for catechols still was positive and 1 ml (8.69 mmol) benzyl chloride, 1.06 g K\textsubscript{2}CO\textsubscript{3} and 140 mg NaI were added to the mixture and refluxed for another 10 h. Removal of the THF under vacuum was followed by redissolving the residue in H\textsubscript{2}O/ether. The layers were separated and the aqueous layer was extracted twice with ether. The ether extracts were combined, washed twice with H\textsubscript{2}O, dried over
MgSO$_4$ and purified by flash chromatography using 30% ethyl acetate in hexane as eluting solution. Crystallization in CH$_2$Cl$_2$/hexane gave 0.642 g (54%) of white crystalline dibenzylxoxyphenylacetonitrile 58.

mp = 69-70°C

$^1$H NMR (CDCl$_3$):

7.51-7.28 (m, 10H, Ar-H)

7.19-6.67 (m, 2H, Ar-H)

5.10 (s, 4H, Ar-CH$_2$O)

3.65 (s, 2H, Ar-CH$_2$CN)

IR (KBr) cm$^{-1}$: 2250 (C≡N)

MS: 347 (M$^+$), 91 (base)

Analysis for C$_{22}$H$_{18}$NO$_2$F

Calculated: C, 76.07; H, 5.22; N, 4.03; F; 5.47;

found: C, 75.86; H, 5.29; N, 4.00; F; 5.47.
Ethyl-2-(2'-fluoro-3',4'-dibenzyloxyphenyl)iminoacetate hydrochloride (59)

The iminoacetate 59 was prepared in a similar manner as iminoacetate 55 but for the following modifications:

Nitrile 58 = 1.18 g (3.22 mmol)
benzene = 5 ml
ethanol = 0.25 ml (4.26 mmol)
HCl = 0.22 g

White crystalline iminoacetate 59 = 1.291 g (93%)
mp = 107-108°C
2-(2'-Fluoro-3',4'-dibenzylxymethyl)imidazoline hydrochloride (60)

The imidazoline 60 was prepared in a similar manner as imidazoline 54 but for the following modifications:

Iminoacetate 59 = 1.096 g (2.55 mmol)

CH₂Cl₂ = 6 ml

Ethylenediamine = 0.5 ml (7.48 mmol)

Crystallization using CH₂Cl₂/hexane gave 0.731 g (73%) of the free base of the imidazoline 60 as a white crystalline material.

mp = 98-99°C

HCl salt of 670 mg (1.72 mmol) was made and crystallization using CH₂Cl₂/benzene/ether gave 0.598 g (82%) of white crystalline imidazoline 60.

mp = 104-105°C

¹H NMR (CDCl₃):

7.37-7.30 (m, 10H, Ar-H)

7.24-6.69 (m, 2H, Ar-H meta & para to F)

5.07-5.05 (d, 4H, Ar-CH₂-O)

4.04 (s, 2H, Ar-CH₂-C)

3.76 (s, 4H, NCH₂CH₂N)
IR (KBr) cm$^{-1}$: 3485, 3420 (NH), 1610 (C=\(\text{-}\text{N}\))

MS: 390 (\(\text{M}^+ - \text{HCl}\)), 91 (base)

Analysis for \(\text{C}_{24}\text{H}_{24}\text{N}_2\text{O}_2\text{FCl}\)

Calculated: C, 67.52; H, 5.67; N, 6.56; F, 4.45;
found: C, 67.22; H, 5.88; N, 6.47; F, 4.57.

\textit{2-(2'-Fluoro-3',4'-dihydroxybenzyl)imidazoline hydrochloride (36)}

Hydrogenation of 255 mg (0.60 mmol) of the dibenzylimidazoline 60 in 20 ml ethanol using 35 mg 10% Pd/C as catalyst was carried out at 40 psi for 2.5 h. Filtration to remove the Pd/C was followed by concentrating the filtrate to a small volume and filtering it over Celite to remove any traces of Pd/C. Crystallization using ethanol/CH$_2$Cl$_2$/pentane gave 101 mg (69%) of catecholimidazoline 36.

mp = 222-223°C

$^1\text{H} \text{ NMR (D}_2\text{O)}$:

6.67-6.64 (m, 2H, Ar-H)

3.81 (br s, 6H, Ar-CH$_2$, NCH$_2$CH$_2$N)

IR (KBr) cm$^{-1}$: 3360 (NH), 3210, 3120 (OH)
MS: 210 (M⁺ - HCl), 141 (base)

Analysis for C₁₀H₁₂N₂O₂FCl

Calculated: C, 48.69; H, 4.90; N, 11.36; F, 7.70;
found: C, 48.90; H, 5.08; N, 11.19; F, 7.58.

2-Fluoro-3,4-dimethoxybenzaldehyde (48)

Method a)

To a solution of 0.14 g (6.09 mmol) sodium in 5 ml dry, absolute ethanol was added 0.55 ml (6.12 mmol) 2-nitropropane then 1.00 g (4.88 mmol) of the benzylic halide 45 and the reaction mixture was stirred at RT for 4 h. The mixture was then filtered and the ethanol removed under pressure. The residue was redissolved in 10 ml ether and 5 ml H₂O. The layers were separated and the ether layer was washed twice with 5 ml 10% NaOH, twice with 5 ml H₂O and dried over Na₂SO₄. Purification by column chromatography using 15% ethyl acetate in hexane as eluting solution gave 0.44 g (49%) of the desired aldehyde 48.
Method b)

A mixture of 3.908 g (19.10 mmol) of the benzylic halide 45, 2.34 g (27.85 mmol) NaHCO$_3$ and 30 ml DMSO was heated and maintained at 100°C for 7.5 h after which TLC showed the reaction to be complete. The reaction mixture was cooled down to RT, diluted with H$_2$O and extracted 5 times with ether. The combined ether extracts was washed three times with H$_2$O, dried over MgSO$_4$ and purified by flash chromatography using 20% ethyl acetate in hexane as eluting solution. Crystallization in CH$_2$Cl$_2$/hexane gave 2.94 g (84%) of aldehyde 48 as white crystalline needles, mp = 51-52°C (lit. m.p. = 52.5-53.5°C).

$^1$H NMR (CDCl$_3$):

- 10.20 (s, 1H, O=CH)
- 7.69-7.51 (m, 1H, Ar-H)
- 6.86-6.76 (m, 1H, Ar-H)
- 3.96 (s, 6H, Ar-CH$_3$)

IR (KBr) cm$^{-1}$: 1670 (C=O)

MS: 184 (M$^+$, base)
To a solution of 1.083 g (5.88 mmol) of the aldehyde 48 in 5 ml CH₂Cl₂ were added 90 mg zinc iodide and 1 ml (7.50 mmol) trimethylsilyl cyanide. The mixture was then stirred at RT for 16 h followed by removal of the solvent under vacuum to give the crude trimethylsilyl cyanohydrin as the residue. To this residue was added 15 ml 3 N HCl and the mixture stirred at RT for 1 h. The product was extracted with ether, washed with water, dried over MgSO₄ and purified by flash chromatography using 30% ethyl acetate in hexane as eluting solution. Crystallization with ethyl acetate/hexane gave 0.90 g (72%) of white crystalline cyanohydrin 61.

mp = 101-103°C

¹H NMR (CDCl₃):

7.37-6.70 (m, 2H, Ar-H)
5.75-5.67 (d, 1H, Ar-CH, J_{HH} = 6.99 Hz, split by OH)
3.95-3.94 (d, 3H, Ar-OCH₃ ortho to F, J_{HF} = 0.95 Hz)
3.91 (s, 3H, Ar-OCH₃ meta to F)
2.89-2.82 (d, 1H, (OH))

IR (KBr) cm⁻¹: 3390 (OH), 2835 (C≡N)
Ethyl-α-hydroxy-2-(2'-fluoro-3',4'-dimethoxyphenyl)iminoacetate hydrochloride (62)

The iminoacetate 62 was prepared in a similar fashion as the iminoacetate 55 but for the following modifications:

Nitrile 61 = 0.5775 g (2.73 mmol)

CHCl₃ = 4 ml
EtOH = 0.20 ml

HCl absorbed = 57 mg

The mixture was then allowed to stand at RT for 30 min and kept in the refrigerator for 16 h to give a viscous liquid. This liquid was allowed to warm up to RT and poured into 10 ml ether during which a white material crystallized to give 0.742 g (92%) of the iminoacetate 62.

mp = 121-122°C
α-Hydroxy-2-(2'-fluoro-3'-4'-dimethoxyphenyl)imidazoline hydrochloride (63)

The imidazoline 63 was prepared in a similar fashion as imidazoline 54 but for the following modifications:

Iminoacetate 62 = 0.5113 g (1.74 mmol)
CH₂Cl₂ = 2 ml
Ethylenediamine = 0.26 ml (3.89 mmol)

Crystallization of the free base from CHCl₃/ether gave 60 mg (14%) of white crystalline material. The HCl salt of 30 mg (0.118 mmol) was made by adding CHCl₃ saturated with HCl to the free base. A white crystalline material was formed. Recrystallization in MeOH/ether gave 26 mg (76%) of imidazoline 63.

mp = 188-190°C

⁴H NMR (free base, CDCl₃)

7.17-6.66 (m, 2H, Ar-H)
5.50 (s, 1H, Ar-CH)
3.93-3.92 (d, 3H, Ar-OCH₃ ortho to F, J_HF = 0.64 Hz)
3.87 (s, 3H, Ar-OCH₃ meta to F)
3.66 (s, 4H, NCH₂CH₂N)
3.00-2.85 (br, 2H, OH, NH)
IR (KBr) cm\(^{-1}\): 3200 (NH), 3100 (OH)

MS: 254 (M\(^+\) - HCl), 184 (base)

Analysis for C\(_{12}\)H\(_{16}\)N\(_2\)O\(_3\)FCl

Calculated: C, 49.58; H, 5.55; N, 9.64; F, 6.53;
found: C, 49.25; H, 5.35; N, 9.36; F, 6.33.

2-Fluoro-3,4-dibenzyl oxybenzaldehyde (70)

![Chemical Structure](https://via.placeholder.com/150)

To 1 ml (10.58 mmol) BBr\(_3\) under argon at RT was added 309 mg (1.68 mmol) of the aldehyde 48 in 2 ml CH\(_2\)Cl\(_2\) drop-wise. The mixture was then allowed to stir at RT for 24 h after which it was cooled with ice-water, and quenched with 5 ml dry methanol. The solvents and trimethyl borate were then removed under vacuum. Methanol was added and the solution evaporated to remove traces of trimethyl borate. The residue was dissolved in 3 ml dry methanol, 0.97 g of Dowex H\(^+\) added, and the mixture was stirred under argon overnight to complete acetal formation. The Dowex resin was removed by filtration then washed with 2 ml methanol. To the filtrate was added 0.8 ml (6.95 mmol) benzyl chloride, 16 mg
potassium iodide, 0.73 g potassium carbonate and the mixture was refluxed under argon for 24 h. The mixture was allowed to cool to RT, 5 ml water added and the methanol removed under vacuum. The aqueous layer was extracted with ethyl acetate (3 × 15 ml) and the combined ethyl acetate fractions were stirred for 1 h with 15 ml 1 N HCl. The layers were separated and the ethyl acetate layer was washed with water, dried over Na₂SO₄ and purified by flash chromatography using 10% ethyl acetate in hexane as the eluting solution. Removal of solvents under vacuum gave a white solid which was crystallized from CH₂Cl₂/hexane to give 147 mg (26%) of aldehyde 70.

mp = 84-85°C

¹H NMR (CDCl₃):

10.15 (s, 1H, O=C-H)
7.55 -7.30 (m, 11H, Ar-H)
6.95 -6.75 (m, 1H, Ar-H)
5.25 (s, 2H, Ar-CH₂-O)
5.10 (s, 2H, Ar-CH₂-O)

IR (KBr) cm⁻¹: 1680 (C=O)

MS: 336 (M⁺), 245, 91 (base)
2-Fluoro-2'-hydroxy-6,3'-dimethoxy biphenyl (74)

A solution of 40.25 g (0.319 mol) m-fluoroanisole in 320 ml dry THF was cooled in a dry ice-acetone bath under an argon atmosphere. To this mixture was added 130 ml (0.338 mol) 2.6 M n-butyllithium in hexane over 10 min. Stirring at -75°C was continued for 5 h during which the solution turned brown. To this mixture was added 35 ml (0.308 mol) trimethylborate in 400 ml ether over 15 min. The cooling bath was removed and stirring continued for 1.25 h. A solution of 210 ml 10% HCl was added slowly, stirring continued for 20 min after which the layers were separated. The organic layer was washed 2 times with H₂O, dried over MgSO₄ and concentrated to give a yellow-orange viscous liquid boronic ester.

The boronic ester was then dissolved in 250 ml toluene and 100 ml 30% H₂O₂ was added. The mixture was heated and allowed to reflux for 45 min. After cooling down to room temperature, the layers were separated. The organic layer was washed once with H₂O, twice with 10% ferrous ammonium
sulfate and again with H$_2$O. The toluene layer was extracted twice with 10% NaOH. While cooling with ice-water, the combined NaOH extracts was acidified with concentrated HCl. Two extractions with CH$_2$Cl$_2$ was followed by drying the combined extracts over MgSO$_4$, passing the solution over Norit A decolourizing carbon and concentrating to give a dark-red crude phenol. Purification was done by flash chromatography, eluting with 20% ethyl acetate in petroleum ether. Removal of solvents under vacuum gave 14.35 g (36%) of a light yellow viscous liquid phenol which crystallized to give white crystalline material. Recrystallization was carried out in ether/hexane to give biphenyl phenol 74 as white crystalline material.

\[ \text{mp} = 74-76^\circ C \]

$^1$H NMR (CDCl$_3$)

7.45-6.70 (m, 6H, Ar-H)
5.72 (s, 1H, Ar-OH)
3.92 (s, 3H, Ar-OCH$_3$)
3.79 (s, 3H, Ar-OCH$_3$)

IR (KBr) cm$^{-1}$: 3500 (OH)

MS: 248 (M$^+$, base)

Analysis for C$_{14}$H$_{13}$O$_3$F

Calculated: C, 67.74; H, 5.23; F, 7.65;

found: C, 67.64; H, 5.39; F, 7.62.
A mixture of 3.50 g (14 mmol) of phenol 74 in 50 ml dry acetone, 10.00 g (72.4 mmol) granular anhydrous K₂CO₃, 7.5 ml (79.3 mmol) Me₂S0₄ was stirred and refluxed overnight (17 h) after which TLC (silica gel, 20% ethyl acetate in hexane as eluting solution) showed the reaction to be complete. The mixture was cooled to room temperature, diluted with H₂O and extracted twice with ether. The ether extracts were combined, washed twice with H₂O and stirred for 1.25 h with 10% NH₄OH solution. The layers were separated and the organic layer washed thrice with H₂O, dried over MgSO₄ and concentrated to give a white-yellow solid. Crystallization in CH₂Cl₂/hexane gave 3.28 g (89%) of white crystalline biphenyl 76.

mp = 89-90°C

¹H NMR (CDCl₃)

7.45-6.65 (m, 6H, Ar-H)
3.90 (s, 3H, Ar-OCH₃)
3.76 (s, 3H, Ar-OCH₃)
3.65 (s, 3H, Ar-OCH₃)
MS: 262 (M⁺, base), 247

Analysis for C₁₅H₁₅O₃F

Calculated: C, 68.69; H, 5.77; F, 7.24;

found: C, 68.83; H, 5.78; F, 7.49.
SUMMARY

The catecholimidazoline 34 is a potent α-adrenoceptor agonist. This study was directed at the synthesis and pharmacological evaluation of fluorinated analogs of this catecholimidazoline. Knowledge gained from this study include the following:

a) Synthetic entry into fluorinated benzylimidazolines as exemplified by synthesis of compounds 54, 60, 63 and 36. Fluorine coupling of ortho benzylic protons and ortho methoxy protons was found to be about 0-1.3 Hz.

b) Fluorine substitution at the 2' position of catecholimidazoline 34 did not have significant effects on α-adrenergic activity. The catecholimidazoline 34 and the fluorinated isomer 36 have the same level of potency and selectivity on the α-adrenoceptor, being slightly more potent and selective for α2-adrenoceptor.

c) An investigation on the lithiation of m-fluoroanisole, the first reaction in the synthetic entry into fluorinated benzylimidazolines, provided a synthetic entry into fluorinated biphenyls such as biphenyls 74 and 76.
PART II
SYNTHESIS, $\beta$-ADRENERGIC AND ANTIPLATELET ACTIVITIES OF TRIMETOQUINOL ANALOGS
Chapter 5

INTRODUCTION

The discovery, function, mechanism of action as well as subdivision of the adrenergic receptor has been discussed (see Part I, Chapter 1). Drugs acting upon the α-adrenergic receptor formed the subject of Part I and this part concentrates on the β-adrenergic receptor.

Subclassification of the β-receptor based on a comparison of the activities of 15 sympathomimetic amines in four β-receptor systems has been proposed. The β-receptor systems used were lipolysis, cardioacceleration, bronchodilation and vascular relaxation. A distinction of the β-adrenoceptor into two major subtypes namely β₁ (heart, fat cells) and β₂ (bronchi, vascular smooth muscle) was made. Selective β₂ agonists include salbutamol and soterenol. Practolol and butoxamine form examples of antagonists selective for β₁- and β₂-receptors, respectively. Norepinephrine and epinephrine are examples of non-selective agonists whereas propranolol and alprenolol are examples of non-selective antagonists.
\[
\begin{align*}
\text{OH} & \quad \text{OH} \\
& \quad \text{NH-C(CH}_3\text{)}_3 \\
\text{78} \\
& \quad \text{OH} \\
\text{CH}_3\text{-SO-N} & \quad \text{OH} \\
& \quad \text{NH-CH(CCH}_3\text{)}_2 \\
\text{79} \\
& \quad \text{O} \\
\text{CH}_3\text{-C-HN} & \quad \text{OH} \\
& \quad \text{NH-CH(CCH}_3\text{)}_2 \\
\text{80} \\
& \quad \text{OH} \\
\text{CH}_3\text{O} & \quad \text{NH-C(CH}_3\text{)}_3 \\
\text{81}
\end{align*}
\]
The fundamental difference between $\beta_1$- and $\beta_2$-adrenoceptors has not yet been elucidated.\textsuperscript{62,63} It remains to be established whether the differences are due to chemical nature of the receptors, lipoproteins involved in communication between each receptor and adenyl cyclase or in the catalytic unit.

One of the effects of $\beta_2$-receptor agonists is bronchodilation and thus are used in the treatment of bronchial asthma. The mechanism of action of these $\beta_2$-agonists have been examined\textsuperscript{65} and are shown in Figures 4 and 5. They stimulate adenylate cyclase and lead to increase of intracellular cAMP (Figure 4). Increase in cAMP levels produces the relaxation of lung smooth muscle.\textsuperscript{59,65} and stabilizes mast cells thus inhibiting degranulation or the release of agents such as histamine, slow reacting substance of anaphylaxis (SRS-A) and serotonin which may lead to bronchoconstriction (Figure 5).\textsuperscript{59,65,66} On the other hand, acetylcholine is thought to promote bronchoconstriction by binding to cholinergic receptors which results in stimulation of guanylate cyclase and consequently cGMP which may be involved in stimulating degranulation of sensitized mast cells.\textsuperscript{59,67}

Tetrahydroisoquinolines (THIs) represent a new class of cyclized phenethylamines whose pharmacological properties are now being realized. Appropriately substituted THIs have
Figure 4: Mechanism of Bronchodilation by $\beta_2$-Agonists
Figure 5: Mechanism of Inhibition of Bronchoconstriction by $\beta_2$-Agonists
shown a variety of pharmacological actions which include lipolytic, bronchial relaxant, hypotensive, platelet antiaggregatory, cardiostimulant and uterine stimulant properties. One of the earliest reports of hypotensive activity of THIs was by Laidlaw in 1910 using 1-(3',4'-dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (tetrahydropapaveroline). Tetrahydropapaveroline has been shown to exhibit β-adrenoceptor stimulant properties. This drug acts directly on β-adrenoceptors since it is unaffected by reserpine but blocked by β-adrenoceptor blocking agents. The structural requirements for potent bronchodilating activity in the THI series have been proposed to include the 1,2,3,4-THI nucleus, the catechol hydroxy groups at the 6 and 7 positions and an arylmethyl group at the 1 position. Moreover, the nitrogen atom, catechol nucleus and aromatic ring of the arylmethyl group at the 1 position are the important groups in the interaction of these drugs with the β-adrenoceptor.
The fact that tetrahydropapaveroline had appreciable bronchodilating activity led to the synthesis and evaluation of this structurally related to this agent. One of the compounds synthesized in this study was 1-(3',4',5'-tri-methoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (trimetoquinol, TMQ). This compound was shown to be one of the most potent β-adrenoceptor stimulants examined thus far. Its activity can be blocked by β-antagonists such as propranolol. In a study of lipolysis by TMQ and nor-epinephrine, competitive inhibition by propranolol was demonstrated to occur to about the same degree, demonstrating binding to the same receptor by both compounds. It is approximately ten times more active than the classical β-adrenoceptor agonist isoproterenol in some β-receptor
preparations for example the guinea pig tracheal relaxation system.\(^7\) It also has been used as a bronchial relaxant (marketed under the tradename Inolin\(^8\)) in Japan.

However, TMQ has been shown to be a non-selective \(\beta\)-stimulant\(^5\) being equipotent in heart and trachea.\(^6\) Structure activity relationship studies have been performed on TMQ. It follows the general guidelines for \(\beta\)-adrenoceptor activity of THI discussed above thus the catechol group, nitrogen atom and arylmethyl group at position 1 have been postulated as being necessary for activity by Iwasawa and Kiyomoto.\(^7\) Among the structural differences in comparison to the classical catecholamines is the lack of a \(\beta\)-hydroxy group. An asymmetric carbon does exist at position 1 although this center of asymmetry differs from the center of asymmetry in norepinephrine, isoproterenol and related catecholamines. Stereoselective interaction of TMQ with \(\beta\)-adrenoceptor has been demonstrated by Miller, Feller et al.\(^6\),\(^7\),\(^3\),\(^7\),\(^6\),\(^8\) and by Buckner and Abel.\(^5\) Unlike with norepinephrine and isoproterenol where optimal \(\beta\)-adrenoceptor activity was found to reside in the R-(-)-isomer, the S-(-)-TMQ \(^8\) was found to be the more active isomer. The relative potency of these compounds as \(\beta\)-adrenoceptor agonists\(^6\) has been found to be: S-(-)-trimetoquinol \(^8\) > R-(-)-isoproterenol \(^8\) > R-(-)-norepinephrine \(^8\).
The synthesis and pharmacological evaluation of several TMQ analogs including the fragmented, seven membered ring and several analogs with substitution on the TMQ have been described. Such analogs of TMQ include compounds 90-114. In this series, the basic ring structure of TMQ was maintained. Effect of dissubstitution at C-1 was examined by synthesis and evaluation of 1-methyl-TMQ 90 and 1-benzyl-TMQ 91. Compound 90 incorporated salsolinol 115 in TMQ. Salsolinol has been reported to have both direct and indirect $\beta$-agonist activity. 85,91,92 Both 1-methyl-TMQ and 1-benzyl-TMQ are inactive as $\beta_2$-agonists and in fact the
latter was found to be a selective $\beta_1$-antagonist in guinea pig atria. 88

\[ \text{Chemical structures} \]

Substitution on position 4 giving compounds 92 and 93, or transposition of the trimethoxy groups\(^{58,93}\) to get a 2,3,4-arrangement compound as in 94 all lead to decrease in $\beta_2$-agonist potency and selectivity when compared to TMQ especially $S$-(-)-TMQ. Transposition of the catechol hydroxy groups to give a 5,7-dihydroxy other than the 6,7-dihydroxy substitution of TMQ resulted in compound 95 with twice the bronchial dilating activity\(^{94,95}\) and improved the bioavailability when administered intraduodenally.\(^{96}\) Substitution at the $\alpha$-position (the 3,4,5-trimethoxybenzylic position) has
92 \( R = \text{CH}_2\text{Ph} \)

93 \( R = \text{3,4,5-Trimethoxybenzyl} \)
been examined by Miller and Feller. Substitution of a hydroxy, methyl or isopropyl all gave stereoisomers which could be separated to give compounds and evaluated. Both isomers with hydroxy substitution were less active than TMQ in both $\beta_1$- and $\beta_2$-adrenoceptors. The $\alpha$-methyl threo isomer is more active and selective on $\beta_2$ adrenergic receptors than TMQ though the erythro isomer was less active than TMQ in both $\beta$-adrenoceptor systems. The isopropyl group analogs were also less active. Dimethyl substitution provided an isomer that was 6000 times less active than TMQ. Cyclic substitution to give compounds or inserting a $\text{CH}_2$ to give compound also led to a decrease in activity.

Expansion of the THI nucleus to give the tetrahydrobenzazepine analogs has also been examined. This modification gave compounds with decreased $\beta$-adrenoceptor agonist activities and even antagonists. Miller and Feller as well as Iwasawa and Kiyomoto have examined various fragmented derivatives of TMQ and found only weak $\beta$-adrenoceptor agonist activity in such analogs. Some of these analogs are compounds. However, the analogs retaining the basic TMQ structure but with further substitution on the nitrogen atom have not been fully explored.
The growing importance of ring-fluorinated catecholamines formed the basis of Part I. Ring fluorination on noradrenaline was used to obtain selectivity between α- and β-receptors and to investigate the importance of the catechol hydroxy groups as well as electron distribution on the phenyl ring. Since the dramatic results obtained for noradrenaline was not observed in the case of dopamine, the selectivity observed was later ascribed to rotamer stabilization due to hydrogen bonding between fluoride and the β-hydroxy group. The β-hydroxy group is the only difference between norepinephrine and dopamine. Ring fluorination study has been extended to the known β-adrenoceptor agonist, isoproterenol. Here, it was found that the 2- and 5-fluoro isomers were equipotent with the parent compound whereas the 6-fluoro isomer was devoid of β-activity. No significant α-adrenoceptor activity could be detected for any of the fluoroisoproterenols. The apparent fluorine-induced effects were shown to be at the receptor binding site by conducting radioligand binding assay experiments. However, this exciting ring-fluorination work has not been extended to the THI class.

Many compounds including azaprostacyclins and trimetroquinol also have been found to be potent inhibitors of platelet aggregation. Platelets are disc-shaped cells
contained in the bloodstream. The aggregation of platelets on walls of arteries is postulated to be involved in the development of arteriosclerosis. Hypertension and arteriosclerosis are believed to be the major etiological processes in the development of cardiovascular diseases, a major health concern. A mechanism for the development of arteriosclerosis, a progressive coronary artery disease, is thought to involve platelet aggregation on a lesion in walls of arteries. It has been suggested that platelets may be involved in initiating the lesions. The aggregated platelets can then undergo biochemical reactions which may initiate and result in the build-up of fibrous and fatty matter. Subsequently, this build-up leads to narrowing, vessel occlusion and potentially stroke or myocardial infarction. The development of a means for monitoring and preventing platelet interactions with injured vessels could play a major role in the prevention of arteriosclerotic vascular disease.

Polyunsaturated fatty acids such as arachidonic acid and its prostaglandin, thromboxane and prostacyclin metabolites shown in Figure 6 play a major role in the control of arterial wall and platelets. Thromboxane $A_2$ ($\text{TXA}_2$) aggregates while prostacyclin ($\text{PGI}_2$) disperses platelets. This is depicted in Figure 7. An imbalance
Figure 6: Metabolic Pathways for Arachidonic Acid, (modified from Gorman et al.).
Figure 7: Regulation of Human Platelet Aggregation by PGI₂ and TXA₂ (modified from Gorman et al).106
in TXA₂ and PGI₂ may be involved in the process of thrombosis and perhaps arteriosclerosis at the arterial cell surface.¹⁰⁷

A diversity of other agents have been found to initiate platelet aggregation.¹⁰⁸ These include proteins (collagen), proteolytic enzymes (thrombin), adenosine diphosphate (ADP) and epinephrine. Basically, they all cause platelets to undergo an initial rapid shape change, release materials such as ADP, serotonin and calcium¹⁰⁹ stored in granular cell components and ultimately aggregate. Four biochemical modes of platelet aggregation have been identified. A possible common denominator for these processes could be an increase in intracellular calcium.¹¹⁰ These pathways are discussed below and illustrated in Figure 8.

a) The ADP pathway:

Binding of ADP to the platelet surface causes exposure of fibrinogen receptors and the binding of fibrinogen to these receptors facilitates cross-linking of platelet.¹¹¹,¹¹² ADP stimulation of microtube disassembly and inhibition of adenylate cyclase¹¹³,¹¹⁴ are thought to be contributing factors.
Figure 8: Proposed Platelet Aggregation Pathways (modified from Navran).
b) **The Platelet Activating Factor (PAF) pathway:**

Platelet activating factor (PAF), 1-O-alkyl-2-acetylglyceryl-3-phosphorylcholine is a substance released from platelets by calcium ionophore A-23187, collagen, thrombin or immune stimulation.\(^{116}\) In the presence of nonsteroidal anti-inflammatory drugs (which inhibit the synthesis of prostaglandins), creatinine phosphate (which scavenges ADP), PAF can still induce platelet aggregation suggesting another mode of platelet aggregation.

c) **The phospholipase C pathway:**

Thrombin, a proteolytic enzyme, can stimulate platelet aggregation via prostaglandin dependent and independent pathways.\(^{118,119}\) This action of thrombin is also not inhibited by ATP, an inhibitor of ADP-induced aggregation.\(^{120}\) Recent studies indicated that thrombin stimulates a phosphotidylinositol specific phospholipase C in platelets.\(^{121,122}\) This enzyme converts the breakdown of phosphatidylinositol to diacylglycerol which is further phosphorylated to form phosphatidic acid.\(^{123}\) The turnover of phosphatidylinositol to diacylglyceride and then to phosphatidic acid has been linked to intracellular
calcium mobilization and ultimately platelet aggregation.\textsuperscript{124,125}

d) \textbf{The prostaglandin pathway:}

In addition to recognized therapeutic effects, aspirin and similar drugs produce a variety of side effects such as inhibition of platelet adhesiveness leading to a prolonged bleeding time.\textsuperscript{126} It is now known that aspirin interferes with arachidonic acid biochemical cascade leading to biosynthesis of prostaglandins, thromboxanes and similar fatty acids. ADP, epinephrine or collagen-induced aggregation is due to the stimulation and release of arachidonic acid from cell membrane phospholipids by activating phospholipase A\textsubscript{2}\textsuperscript{127} or phospholipase C-diglyceride lipase sequence.\textsuperscript{128} Released arachidonic acid \textsuperscript{116} is converted by cyclooxygenase (blocked by aspirin) to prostaglandin endoperoxides PGG\textsubscript{2} \textsuperscript{120} and then PGH\textsubscript{2} \textsuperscript{121,129} which in turn is rapidly converted by thromboxane synthetase to TXA\textsubscript{2} \textsuperscript{130} as shown in Figure 6. Though the prostaglandin endoperoxides have little or no platelet aggregatory activity,\textsuperscript{106} TXA\textsubscript{2} is a potent platelet aggregating agent.\textsuperscript{131}
The antiaggregatory activity of TMQ is independent of β-adrenergic agonist activity. R-(+)-TMQ is the more potent isomer in inhibiting platelet aggregation mediated through ADP or prostaglandin-related pathways. R-(−)-TMQ has been proposed to act as a competitive inhibitor of TXA$_2$ at the level of the TXA$_2$ receptor. However, in phospholipase C or low dose thrombin-induced platelet aggregation which are independent of prostaglandin mediation, S-(−)-TMQ is about three times more active than R-(+)-TMQ in inhibiting this aggregation.

Again, as in the case of SAR studies done for β-agonist activity, most of the analogs of TMQ examined thus far have shown a lower activity than R-(+)-TMQ in inhibiting platelet aggregation. The N-substituted TMQ analogs also have not been extensively studies. No TMQ alkylating agent derivative has yet been made to see if irreversible alkylation to the TXA$_2$ receptor can be achieved. This will help in clarifying the mode of antiaggregatory activity of TMQ. The effects of fluorinated TMQ analogs also have not been examined.
Chapter 6

STATEMENT OF PROBLEMS AND OBJECTIVES

Phenethylamines form an important class of drugs that interact with the adrenergic receptor. The adrenergic receptor has been divided into α- and β-adrenergic receptors depending upon pharmacological activity mediated by the receptor. Subdivision of the β-adrenoceptor into β_1- and β_2-systems has resulted in the development of agents selective for stimulating heart muscle or lipolysis (β_1) or for promoting bronchodilation or vasodilation (β_2).

Tetrahydroisoquinolines represent a class of cyclized phenethylamines whose pharmacological properties are being realized. Trimetoquinol (TMQ) 86, a tetrahydroisoquinoline, has been shown to be a potent but non-selective β-adrenoceptor agonist. 58,103 It is used in Japan for relief of asthmatic bronchospasms. 75 The bronchodilating properties are associated with stimulation of β-adrenoceptors in the tracheal muscle. The side effects such as cardiotimulant and tremorigenic activities which are due to the lack of selectivity for β_2-adrenoceptor may limit or preclude its use as a bronchodilator in the treatment of asthma.
Both isomers of TMQ \([R-(+\) and S-(-)]\) have been shown to inhibit platelet aggregation by inhibiting the phospholipase C-mediated aggregation pathway. Furthermore, \(R-(+)-TMQ\) is thought to also act by antagonizing \(TXA_2\) at its receptor.

The objective of this investigation was to synthesize several \(N\)-substituted TMQ derivatives. These will then be evaluated for intrinsic activity, potency and selectivity in the \(\beta\)-adrenergic receptor systems and for ability to inhibit platelet aggregation. Compounds 134, 138, 143, 148 and 150 have been proposed as suitable targets for achieving this goal. Specifically, the alkylating agent 138 has been designed to investigate if irreversible binding to the receptor mediating platelet aggregation can be achieved.

The reasons for and growing importance of ring fluorinated catecholamines has been discussed above (See Part I and the preceding chapter [Chapter 5]). Kirk and coworkers have shown that fluorine substitution at position 2 of noradrenaline leads to a molecule that is selective for \(\beta\)-adrenoceptor unlike the parent molecule which is non-selective between \(\alpha\)- and \(\beta\)-adrenergic receptors. Furthermore, they have taken a known \(\beta\)-adrenergic receptor agonist, isoproterenol put fluorine at position 2 to obtain an analog which is more potent than the parent compound as a
β-adrenoceptor agonist. However, they were not able to detect selectivity between \( \beta_1 \)- and \( \beta_2 \)-adrenoceptors. Compound 155 has been designed to examine the analogous situation in the THIs class. Fluorine substitution at position 5 of TMQ is analogous to fluorine substitution at position 2 of norepinephrine or isoproterenol. This fluorinated TMQ could serve to determine if potency and/or selectivity between \( \beta_1 \)- and \( \beta_2 \)-adrenergic receptors could be obtained by ring fluorination in this class. Again, the effects of fluorine substitution on ability to inhibit platelet aggregation will be evaluated. These will shed some light on the relative importance of the acidity of the catechol hydroxy groups and perturbation of the electronic properties of the catechol ring on the biological activity of TMQ.

Though much of the chemistry involved in the synthesis of the proposed compounds seem to be straightforward, several steps seem to be worth discussion. In the synthesis of the N-substituted TMQ derivatives, a procedure for the selective cleavage of two O-benzyl groups to give a catechol in the presence of an N-benzyl group and several O-methyl groups has to be developed. In the fluorinated TMQ investigation, the major goals would be synthesis of the fluorinated dibenzyloxyphenethylamine 151. This compound could
become a very useful synthetic intermediate. Investigation of the Bischler-Napieralski cyclization under forcing conditions, specifically cyclization of the amide 153 would be attempted and would examine if fluorine substitution could possibly retard a Bischler-Napieralski reaction to the point of preventing it. 132,133
Chapter 7
RESULTS AND DISCUSSION

CHEMISTRY

This will be discussed under six categories and in the order listed below.

1. Synthesis of TMQ (86)
2. Synthesis of N-benzyl TMQ (134)
3. Synthesis of N-β-hydroxyethyl TMQ (143) and N-β-chloroethyl TMQ (138)
4. Synthesis of N-methyl TMQ (148)
5. Synthesis of N-ethyl TMQ (150)
6. Approach to 5-fluoro TMQ (155)

Synthesis of TMQ (86)

Synthesis of TMQ was carried out in a similar fashion as previously reported by this laboratory \(^{82,134}\) but with a few modifications. The new approach is shown in Scheme VII. The amide 129 which is a key intermediate in all the synthesis of TMQ and derivatives was formed in 75% yield by condensation of the free base of the phenethylamine 127 and acid 128 directly and azeotropically removing the water.
formed using a Dean-Stark trap. This served to push the equilibrium in the desired direction. This entry to amide 129 is an improvement over the previous manner which involved two steps and goes in 56% yield. Bischler-Napieralski cyclization of amide 129 to obtain the unstable imine 130 was followed by reduction of this imine with NaBH₄ and making the HCl salt to give the crystalline amine salt 131 in 72% yield. It is imperative that the imine 130 be exposed to the minimum amount of air possible as it has been shown to oxidize in air⁹⁸,¹³⁴ to give the ketone 130a as shown in Equation 3. This type of oxidation also has been reported for other 1-benzylidihydroisoquinolines.¹³⁵,¹³⁶
SCHEME VII

XIIa

127

\[
\begin{align*}
\text{PhCH}_2\text{O} & \text{PhCH}_2\text{O} \\
\text{NH}_2 &
\end{align*}
\]

1. NaHCO₃

2. COOH

\[
\begin{align*}
\text{CH}_2 & \\
\text{OCH}_3 & \\
\text{OCH}_3
\end{align*}
\]

128

\[
\begin{align*}
\text{PhCH}_2\text{O} & \text{PhCH}_2\text{O} \\
\text{CH}_2 &
\end{align*}
\]

1. NaBH₄

2. HCl

\[
\begin{align*}
\text{PhCH}_2\text{O} & \text{PhCH}_2\text{O} \\
\text{CH}_2 & \\
\text{OCH}_3 & \\
\text{OCH}_3
\end{align*}
\]

130

\[
\begin{align*}
\text{H}_2, \text{Pd} / \text{C}
\end{align*}
\]

131

\[
\begin{align*}
\text{PhCH}_2\text{O} & \text{PhCH}_2\text{O} \\
\text{NH}_2 &
\end{align*}
\]

86
XIIb
The mechanism of the Bischler Napieralski cyclization has been investigated by Fodor \textsuperscript{132} and Castagnoli \textsuperscript{133}. This reaction was shown to proceed through a nitrilium ion, the same intermediate proposed in the von Braun degradation of amides. Once formed, the nitrilium ion can undergo at least two other reactions besides the desired cyclization. Castagnoli and coworkers isolated and characterized the products from these other reactions including the nitrile and halide that would be expected by the von Braun degradation.

A proposed mechanism for the cyclization of amide \textsuperscript{129} is shown in Scheme VIIb. Obviously, the "good nucleophilicity" \textsuperscript{132,133} of the aromatic ortho carbon (C-6 on amide \textsuperscript{129}) and the relative instability of the cation that would be formed by cleavage of the C-N to give the von Braun products led to a high yield of the desired product. The NaBH\textsubscript{4} reduction was carried out in ethanol rather than methanol \textsuperscript{98,134} since too much bubbling was observed in the latter solvent. Hydrogenation of the amine salt \textsuperscript{131} using 10\% Pd/C as catalyst gave trimetoquinol \textsuperscript{86} in 82\% yield. Again, the hydrogenation was carried out in ethanol as opposed to methanol. Use of methanol in hydrogenations with heterogeneous catalysis involves a much higher fire hazard.
Synthesis of N-benzyl TMQ (134)

Synthesis of N-benzyl TMQ 134 was performed as shown in Scheme VIII. The imine 130, obtained by cyclization of amide 129, was reacted with benzyl bromide to give the crystalline imine salt 132. Reduction of the imine salt with NaBH₄ was followed by making the HCl salt of the amine to give the amine salt 133. Several attempts to selectively cleave off the O-benzyl groups in the presence of N-benzyl group were made. Some of the systems tried are hydrogenation using Pd/C or Pd/BaSO₄ 137-139 as catalyst, Me₃SiI 140,141 and BCl₃. 141 Use of 10% Pd/C at 45 psi for 16 h or 5% Pd/BaSO₄ at atmospheric pressure for 10 h both gave TMQ. Attempt to monitor the hydrogenation using Pd/BaSO₄ as catalyst as well as the Me₃SiI and BCl₃ reactions gave complex mixtures and this work was not pursued. The mixtures probably correspond to the several debenzylation combinations possible and perhaps demethylations in the latter two cases.

During this study, the attempt to perform chloromethylation on 2,3-dibenzoyoxyfluorobenzene 56 was done (see Part I, page 38). The conditions for the reaction involved bubbling HCl gas to the fluorobenzene in acetic acid. It was noticed that the benzyl protecting groups were probably cleaved off under this condition. Extension of this
observation to see if it can be useful for the desired se-
lective cleavage in the case of compound 131 was then at-
tempted. After trying several HCl-solvent systems and con-
ditions, a best system which involved refluxing amine salt
131 in a 50:50 mixture of concentrated (37%) HCl and metha-
nol was discovered. Reflux for 32 h gave the desired N-ben-
zyl TMQ in 99% yield. This molecule always crystallized
with solvent used for crystallization which could be ethanol
or tetrahydrofuran.

Although further search in literature revealed prece-
dence for cleaving off an O-benzyl group to give a phenol by
this method, this may be the first report to obtain a
catechol in this manner and to obtain the type of selectivi-
ty described using this system.

Confirmation that the desired catechol 134 was obtained
was done by acetylation the catechol product, character-
izing the diacetyl derivative 135, obtained in 49% yield as
a white crystalline material and reconverting it back to the
catechol 134 by simple ester hydrolysis. The product ob-
tained by ester hydrolysis and that obtained by direct de-
benzylation were shown to be identical.

Acetylation was performed using 4-dimethylaminopyridine
(DMAP) as catalyst. This has the advantages of shorter
reaction time and easier purification of product over the
SCHEME VIII

Villa

1. $\text{POCl}_3$
2. $\text{PhCH}_2\text{Br}$

1. $\text{NaBH}_4$
2. $\text{HCl}$

$\text{HCl, } \Delta$

129

132

133

134
VIIIb

134 \[ \rightarrow \]

1. (CH₃)₂O

DMAP

2. HCl

H₂O, HCl

135
conventional acetylating procedure. Any other acetylated derivative (mono, di or tri ester/amide or any permutation thereof) other than the proposed 135 will certainly not agree with the observed data thus confirming that the catechol 134 was obtained as predicted earlier on.

Synthesis of N-β-hydroxymethyl TMQ (143) and N-β-chloroethyl TMQ (138)

The synthetic approaches to these compounds are shown in Scheme IX. The amine salt 131 reacted with chloroacetic anhydride in the presence of Na₂CO₃ to give the amide 136 in 85% yield. However, Scheme IXa to the β-chloroethyl TMQ 138 was abandoned since the amide 136 could not be successfully reduced to give the β-chloroamine 137. Diborane reduction of the amide 136 gave a complex mixture from which the only isolatable material was the amine 139 where both the carbonyl group and the chlorine got reduced. Reduction attempts with triethylsilane and trichlorosilane were not successful.

Another approach to the β-chloroethyl TMQ shown in Scheme IXb was abandoned because the first step which involved the Bischler-Napieralski cyclization to give the imine 130 followed by reaction with bromoethanol was not successful. However, it is believed that this reaction may
still produce the desired product upon further exploration of the reaction conditions. This scheme was abandoned for a similar scheme directed at obtaining the amine alcohol 141. The new method involved reacting the free base of amine salt 131 with bromoethanol\textsuperscript{149,150} to give the free base of amine alcohol 141. After trying several reaction conditions, one that gave the desired product was finally obtained. Purification of the product proved to be difficult and the amine alcohol could only be crystallized as the oxalate salt 142.

Another way of obtaining the amine alcohol 141 was explored. Reaction of the free base of amine salt 131 with ethylene oxide while cooling at ice-water produced the desired amine alcohol. It is important that the temperature during the first 8 h of this reaction be ice-water temperature; otherwise other compounds which are difficult to separate from the desired amine alcohol also get formed. The HCl salt of the amine alcohol was formed and purified by crystallization to give the amine alcohol salt 141 in 76% yield.

The amine alcohol salt 141 could not be chlorinated to give the β-chloroethyl amine salt 137 by using thionyl chloride (SOCl\textsubscript{2}),\textsuperscript{151,152} phosphorus oxychloride (POCl\textsubscript{3}),\textsuperscript{153} triphenylphosphine/carbon tetrachloride (Ph\textsubscript{3}P/CCl\textsubscript{4})\textsuperscript{154} or methanesulfonyl chloride/lithium chloride/(CH\textsubscript{3}SO\textsubscript{2}Cl/LiCl).\textsuperscript{155} Each system usually resulted in a complex mixture. Therefore, Scheme IXd was abandoned.
SCHEME IX

IXa

\[
\begin{align*}
\text{PhCH}_2\text{O} & \text{NH} \quad \text{PhCH}_2\text{O} \\
\text{PhCH}_2\text{O} & \text{CH}_2 \quad \text{PhCH}_2\text{O} \\
\text{OCH}_3 & \quad \text{OCH}_3 \\
\text{OCH}_3 & \quad \text{OCH}_3
\end{align*}
\]

\[
\text{O} \quad \text{O} \quad \text{O}
\]

\[
\text{Na}_2\text{CO}_3
\]

\[
\text{BH}_3 \text{ or } \text{HSiCl}_3 \text{ or } \text{Et}_3\text{SiH}
\]

\[
\text{H}_2, \text{ Pd/C} \text{ or } \text{BCl}_3
\]

131 \quad 136

137

138
1Xb

1. POCl₃
2. BrCH₂CH₂OH

129

1. NaBH₄
2. HCl

141

1. H₂, Pd/C
2. SOCl₂

138
$\text{PhCH}_2\text{O}$

$\text{PhCH}_2\text{O}$

$\text{CH}_2\text{O}$

$\text{OCH}_3$

$\text{HN}^+\text{Cl}$

$\text{H}^+\text{C}$

$\text{H},\text{HO}$

$\text{Pd/C}$

$\text{H}_2$

$\text{CH}_2\text{O}$

$\text{OCH}_3$

$\text{SOCl}_2$

$\text{H}_2\text{O}$

$\text{OCH}_3$

$\text{CH}_2\text{O}$

$\text{OCH}_3$

$\text{HN}^+\text{Cl}$

$\text{H}^+\text{C}$

$\text{H},\text{HO}$

$\text{Pd/C}$

$\text{H}_2$

$\text{CH}_2\text{O}$

$\text{OCH}_3$

$\text{SOCl}_2$

$\text{H}_2\text{O}$

$\text{OCH}_3$

$\text{CH}_2\text{O}$

$\text{OCH}_3$
Cleavage of the dibenzyl protecting groups of amine alcohol salt 141 gave the catechol β-hydroxy TMQ 143 in 91% yield. Treatment of this with \( \text{SOCl}_2 \) was expected to give the β-chloroethyl TMQ directly. However, another compound, the cyclic sulfite β-chloroethyl TMQ 145 crystallized out in 87% yield during the reaction. This was quite a surprise as a similar reaction in literature was reported to give only the desired β-chloro adduct without \( \text{SOCl}_2 \) reacting with the catechol hydroxy groups. This therefore forms the first reaction of catechols with \( \text{SOCl}_2 \) and the first report of such a cyclic ester ring system. Use of cyclic esters of this type as substrates for nucleophilic substitution in carbohydrate chemistry was recently described. The cyclic sulfur esters were prepared in a similar manner as above except substituting a diol for the catechol. This chemistry certainly needs to be explored to see for example if such sulfur esters can be used to protect catechols or make them undergo certain unique reactions.

The β-chloroethyl TMQ 138 was then obtained by simple aqueous hydrolysis of the sulfur ester 145 followed by lyophilization to give the desired product in 99% yield and as a white solid.
Synthesis of N-Methyl TMQ (148)

Synthesis of N-Methyl TMQ 148 was performed as shown in Scheme X. Cyclization of the amide 129 to give imine 130 was followed by reaction of this imine with methyl iodide to give the imine salt 146 which crystallized out of the reaction solution. This salt was then reduced and the HCl salt formed to give the amine salt 147. This procedure is reminiscent of the procedure for obtaining N-benzyl TMQ 134. The desired N-methyl TMQ 148 was then obtained from the amine salt 127 by hydrogenation or HCl debenzylation following the procedure developed for cleavage of O-benzyl groups in the synthesis of N-benzyl TMQ 134 above. Interestingly, this latter procedure which is simpler and less risky also gave the higher yield 67% as opposed to 61% by hydrogenation.

Synthesis of N-ethyl TMQ (150)

The method of synthesis of N-ethyl TMQ 150 is shown in Scheme XI. The N-acetamide 149 was formed in 65% yield by reacting the free base of compound 131 in the presence of Na₂CO₃ or DMAP with acetic anhydride. This amide was then reduced with diborane and the HCl salt made. Cleavage of the dibenzyl protecting groups with HCl was then done to give the desired N-ethyl TMQ 150.
SCHEME X

1. NaBH₄
2. HCl

H₂, Pd/C or
HCl, Δ
Approach to 5-fluoro TMQ (155)

The synthetic approach to 5-fluoro TMQ is shown in Scheme XII. Synthesis of the nitrile 58 starting material, was discussed in Part I under "Synthesis of 2-(2'-fluoro-3',4'-dihydroxy)benzylimidazoline" (see page 36). Using diborane, this nitrile was reduced to the amine which was then reacted with the trimethoxy phenyl acetic acid 128 to give the key amide 153.

Attempt to cyclize this amide by the Bischler-Napieralski reaction was not successful. This cyclization was carried out only on a 100 mg scale which was too small to be able to make any definitive statements about this reaction. Unquestionably, the presence of the fluorine on position 2 of the amide 153 would definitely retard this reaction since it would decrease the "nucleophilicity" of the aromatic ring on which it is attached. This may lead to a lower yield as there are other competing reactions as described in the synthesis of TMQ above. However, investigations to see if this would lead to a complete halt of Bischler-Napieralski cyclization are yet to be done.

An alternative route to amine salt 151 which could permit scaling up is shown in Scheme XIIb. The nitrile 99, another intermediate in the synthesis of the fluorinated
SCHEME XII

XIIa

1. \( \text{BH}_3 \)
2. \( \text{COOH} \)

1. \( \text{POCl}_3 \)
2. \( \text{NaBH}_4 \)

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

\( 58 \) → \( 128 \) → \( 151 \) → \( 155 \)
XIIb

\[
\begin{align*}
\text{CH}_3\text{O} & \xrightarrow{1. \text{ BH}_3} \text{CH}_3\text{O} \\
\text{CH}_3\text{O} & \xrightarrow{2. \text{ HBr}} \text{CH}_3\text{O} \\
\end{align*}
\]

\[
\begin{align*}
\text{HBr, } \Delta & \xrightarrow{} \\
\text{HO} & \xrightarrow{} \text{HO} \\
\end{align*}
\]
benzylimidazolines was reduced with BH$_3$ and HBr salt was made in 80% yield followed by demethylation in 95% yield using HBr. This led to 2-fluorodopamine 157 which could then be benzylated by the method of Banerjee and Ressler. This method involves protecting the nitrogen with t-butyl carbazate before benzylating. Deprotecting the nitrogen with trifluoroacetic acid and making the HCl salt could then be done to give the amine salt 151.

**BIOLOGY**

Preliminary pharmacological data obtained on the N-substituted TMQ analogs show that the analogs retained both β-adrenergic and antiplatelet aggregatory effects. The cyclic sulfite intermediate 145 in the synthesis of N-β-chloroethyl 138 was also evaluated.

**β-Adrenergic Studies:**

The results of preliminary pharmacologic drug evaluations on carbachol-contracted guinea pig tracheal strips (β$_2$-adrenoeceptor system) and spontaneously beating guinea pig right atria (β$_1$-adrenoeceptor system) are shown in Table 2. As expected, S-(−)-TMQ was considerably more potent.
than R-(+)-TMQ in both β-adrenoceptor systems and only slightly more potent (0.16 to 0.26 log units) than racemic (±)-TMQ. For the N-substituted analogs (134, 143, 145, 138 and 148), it was found that the bigger the N-substituent, the lower the β-adrenergic agonist activity. However, β2-adrenoceptor was able to tolerate this bulk better, leading to a 10-fold difference in activity of the N-benzyl analog 134 in the β-adrenoceptor systems. The rank order as β-adrenoceptor agonist was: S-(−)-TMQ > (±)-TMQ 86 > 148 > R-(+)-TMQ = 143 > 145 > 138 > 134.

Prior incubation (1.5–2 h) of guinea pig atria with 138, followed by a washout did not appear to produce a marked change in concentration response curve of other analogs. This preliminary data indicates that 138 does not give an irreversible alkylation of the β1-adrenoceptor in guinea pig atria. Other studies are needed to verify this observation.
# TABLE 2

Activities of TMQ and N-Analogs on the \( \beta \)-Adrenoceptor

<table>
<thead>
<tr>
<th>Compound</th>
<th>Atrium (( \beta_1 ))</th>
<th>Trachea (( \beta_2 ))</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-((+)-TMQ)</td>
<td>5.58 (0.17)</td>
<td>5.63 (0.10)</td>
<td>4</td>
</tr>
<tr>
<td>S-((-)-TMQ)</td>
<td>7.26 (0.20)</td>
<td>7.23 (0.16)</td>
<td>3</td>
</tr>
<tr>
<td>(\pm)-TMQ (\text{(86)})</td>
<td>7.10 (0.08)</td>
<td>6.96 (0.07)</td>
<td>7</td>
</tr>
<tr>
<td>N-Methyl TMQ (\text{(148)})</td>
<td>5.89 (0.10)</td>
<td>6.05 (0.05)</td>
<td>6</td>
</tr>
<tr>
<td>N-(\beta)-Hydroxyethyl TMQ (\text{(143)})</td>
<td>5.35 (0.01)</td>
<td>5.73 (0.06)</td>
<td>7</td>
</tr>
<tr>
<td>N-(\beta)-Chloroethyl TMQ (\text{(138)})</td>
<td>4.88 (0.10)</td>
<td>5.34 (0.01)</td>
<td>5</td>
</tr>
<tr>
<td>Cyclic sulfite-N-(\beta)-chloroethyl TMQ (\text{(145)})</td>
<td>5.24 (0.14)</td>
<td>5.58 (0.12)</td>
<td>5</td>
</tr>
<tr>
<td>N-Benzyl TMQ (\text{(134)})</td>
<td>4.34 (0.07)</td>
<td>5.34 (0.10)</td>
<td>8</td>
</tr>
</tbody>
</table>

\( pD_2 = -\log ED_{50} \)
Platelet Studies:

The results obtained are shown in Table 3. N-Benzyl TMQ was found to be the most potent in inhibiting both platelet aggregation and secretion of serotonin by U46619 from human platelets. Each of the compounds blocked the aggregatory and secretory responses to U46619, a TXA₂ agonist in human platelets. Using R-(+)-TMQ as a standard antagonist, each analog was less active. The rank order of inhibitory potencies (IC₅₀) for the compounds was: against aggregation: R-(+)-TMQ > S-(−)-TMQ > 134 > 145 > 143 > 138 and against secretion: R-(+)-TMQ > S-(−)-TMQ > 134 > 143 > 138 = 145.

Among the N-substituted TMQ analogs, N-benzyl TMQ 134 was the most active antagonist of aggregation but was about 30-fold less potent than R-(+)-TMQ. Although the compounds appear to act like TXA₂ antagonists as has previously been proposed for the parent drug TMQ, additional work with other stimuli are needed to demonstrate the specificity of their effects.
TABLE 3

Inhibition of Platelet Aggregation and Secretion of $^{14}$C serotonin by trimetoquinol (TMQ) Analogs

The IC$_{50}$ values (µM) and ± standard deviation (in parenthesis) are given below.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Aggregation</th>
<th>Secretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-(+)-TMQ</td>
<td>0.71 (0.16)</td>
<td>0.55 (0.13)</td>
</tr>
<tr>
<td>S-(−)-TMQ</td>
<td>19.3 (2.8)</td>
<td>24.5 (3.0)</td>
</tr>
<tr>
<td>N-Benzyl TMQ (134)</td>
<td>21.2 (0.4)</td>
<td>96.8 (5.7)</td>
</tr>
<tr>
<td>N-β-Hydroxyethyl TMQ (143)</td>
<td>71.6 (3.6)</td>
<td>116.2 (6.9)</td>
</tr>
<tr>
<td>N-β-Chloroethyl TMQ (138)</td>
<td>86.6 (15.3)</td>
<td>162 (28.3)</td>
</tr>
<tr>
<td>Cyclic sulfite-N-β-chloroethyl TMQ (145)</td>
<td>64.2 (5.8)</td>
<td>166.4 (31.1)</td>
</tr>
</tbody>
</table>
Chapter 8
EXPERIMENTAL

The general experimental parameters are given on page 55, at the beginning of Chapter 4. Selected NMR Spectra are shown in Appendix B.

N-3,4-Dibenzyloxyphenethyl-3',4',5'-trimethoxyphenyl acetamide (129)

A solution of 15.70 g (42.4 mmol) of the commercially available 3,4-(Dibenzyloxy)phenethylamine hydrochloride 127 in 100 ml CHCl₃ was extracted three times with 100 ml saturated NaHCO₃ solution and washed with H₂O. The CHCl₃ solution was dried over MgSO₄ and CHCl₃ was removed under vacuum. To the amine residue was added 9.50 g (42.0 mmol)
3,4,5-trimethoxyphenylacetic acid and 100 ml toluene. The mixture was then refluxed for 3 days with azeotropic removal of water using a Dean-Stark trap. It was allowed to cool down and the toluene removed under vacuum. The residue was redissolved in 100 ml CHCl₃ and washed three times with 100 ml 10% HCl, once with 100 ml H₂O, three times with 100 ml saturated NaHCO₃ and twice with 100 ml H₂O. The organic layer was then dried over MgSO₄ and the CHCl₃ removed under vacuum to give the crude amide as a brown solid. The solid was dissolved in hot toluene and allowed to cool down to room temperature. The amide crystallized out of this solution, filtered and washed with ether to give 17.00 g (75%) of a white crystalline material. mp = 109-111°C (lit. mp = 108-109°C)

H NMR (CDCl₃):

7.45-7.28 (m, 10H, Ar-H)
6.85-6.73 (m, 2H, Ar-H)
6.55-6.44 (m, 1H, Ar-H)
6.35 (s, 2H, Ar-H)
5.50-5.35 (br, 1H, NH)
5.12, 5.11 (d, 4H, 2 × Ar-CH₂-O)
3.83 (s, 3H, Ar-OCH₃)
3.78 (s, 6H, 2 × Ar-OCH₃)
3.56-3.30 (m, 4H, Ar-CH$_2$-C)  
2.72-2.56 (t, 2H, CH$_2$-N)  
IR (KBr) cm$^{-1}$: 3320 (NH), 1645 (C=O)  

1-(3',4',5'-Trimethoxybenzyl)-6,7-dibenzyloxy)-1,2,3,4-tetrahydroisoquinoline (131)  

A mixture of 6.4 g (11.8 mmol) of amide 129 in 80 ml dry acetonitrile along with 6 ml (64.4 mmol) POCl$_3$ was refluxed under argon for 3.25 h. The mixture was allowed to cool down followed by removal of solvent and excess POCl$_3$ under vacuum. The resulting residue was dissolved in 100 ml CHCl$_3$, washed once with 100 ml H$_2$O, twice with 100 ml saturated NaHCO$_3$ and twice with 100 ml H$_2$O. The organic layer was dried over MgSO$_4$ and CHCl$_3$ removed using a rotary evaporator. The residue imine oil was dissolved in 80 ml ethanol, cooled in ice-water and 9.0 g (238 mmol) NaBH$_4$ added. The mixture was allowed to warm up to RT and the stirring
under CaCl₂ drying tube continued overnight (16 h). The solvent was removed under vacuum, 100 ml CHCl₃ added to the residue and the resulting solution washed twice with 100 ml 10% NaOH and twice with 100 ml H₂O. The CHCl₃ layer was dried over MgSO₄ and concentrated. HCl gas was bubbled into the remaining solution to make the HCl salt of the amine. The CHCl₃ and excess HCl were removed by rotavap. The residue was redissolved in CHCl₃ and the CHCl₃ removed by rotavap. The residue amine salt was crystallized in CHCl₃/ether to give 4.74 g (72%) of a white crystalline solid.¹⁶⁰

mp = 205-207°C (lit. ¹⁸² mp = 199-202°C)

¹H NMR (CDCl₃, free base):

7.50-7.29 (m, 10H, Ar-H)
6.77 (s, 1H, Ar-H)
6.69 (s, 1H, Ar-H)
6.42 (s, 2H, Ar-H)
5.13 (s, 2H, Ar-CH₂-O)
5.10 (s, 2H, Ar-CH₂-O)
4.11-4.06 (m, 1H, Ar-CH-N)
3.84-3.82 (d, 9H, 3 × Ar-OCH₃)
3.20-2.62 (m, 7H, NH, 3 × CH₂)
L-(3',4',5'-Trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline [Trimetoquinol, TMQ, (86)]

Hydrogenation of 919 mg (1.635 mmol) of amine salt 131 in 40 ml dry ethanol using 168 mg 10% Pd/C as catalyst at 40 psi overnight (16 h) was performed. The catalyst was filtered off and the filtrate concentrated to a small volume, filtered over Celite followed by removal of solvent under vacuum. Crystallization in MeOH/ether gave 514 mg (82%) of light-brown catechol crystals.

FeCl₃ test for catechols: positive

mp = 227-229°C (lit. 74 mp = 225-226°C)

¹H NMR (D₂O):

6.62 (s, 1H, Ar-H)
6.41 (s, 3H, Ar-H)
3.65 (s, 6H, Ar-OCH₃)
3.63 (s, 3H, Ar-OCH₃)
3.30-2.75 (m, 7H, CH, 3 × CH₂)

IR (KBr) cm⁻¹: 3450, 3100 (OH)
The Bischler-Napieralski cyclization was done as in the synthesis of compound 131. Thus 4.00 g (7.39 mmol) of the amide 129, 50 ml dry acetonitrile and 2.0 ml (21.46 mmol) POCl₃ were refluxed under argon for 3 h. Work up was done as before to obtain the imine oil. To the imine in 70 ml benzene, 2.4 ml (20.18 mmol) benzylbromide was added. The mixture was refluxed for 3.5 h under argon during which a yellow solid crystallized. It was then allowed to cool to room temperature, filtered under suction and the crystalline imine salt 132 obtained was washed with ether to give 4.90 g (95%).

mp = 199-202°C (lit. 188 mp = 199-202°C)

To a mixture of 3.30 g (4.75 mmol) of the salt in 100 ml ethanol was added 1.17 g (30.93 mmol) NaBH₄ while cooling with ice-water. The mixture was then allowed to warm up to RT and stirring continued overnight. The ethanol
was removed by rotavap and CHCl₃ added to the residue. The suspension was washed three times with water, dried over Na₂SO₄ and the HCl salt prepared. Crystallization in methanol/ether was done to give 2.85 g (92%) of compound 133 as a white crystalline solid.

mp = 166-168°C

¹H NMR (CDCl₃, free base):

7.41-7.21 (m, 15H, Ar-H)
6.69 (s, 1H, Ar-H)
6.29 (s, 1H, Ar-H)
6.21 (s, 2H, Ar-H)
5.11 (s, 2H, Ar-CH₂-O)
4.92 (s, 2H, Ar-CH₂-O)
3.38 (s, 3H, Ar-OCH₃)
3.75 (s, 2H, Ar-CH₂-N)
3.72 (s, 6H, 2 x Ar-OCH₃)
3.46-2.53 (m, 7H, CH, 3 x CH₂)

MS: 615 (M⁺ - HCl), 434, 181, 91 (base)

Analysis for C₄₀H₄₂NO₅Cl

Calculated: C, 73.66; H, 6.49; N, 2.15;
found: C, 73.39; H, 6.54; N, 2.16.
1-(3',4',5'-Trimethoxybenzyl)-2-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (134)

Method a) (See page 152 for Method b)

To 1.60 g (2.45 mmol) of compound 133 was added 100 ml 50:50 solution of methanol/concentrated HCl and the mixture refluxed for 32 h while stirring under argon. The solvent and excess HCl were removed by rotavap. Methanol was added to the residue and then removed by rotavap. This step was repeated three times. Crystallization in ethanol/ether was done to give 1.14 g (99%) white crystalline 134.

FeCl₃ test for catechols: positive

mp = 160-162°C

An analytical sample was prepared by dissolving 390 mg (0.83 mmol) in H₂O, washing the solution obtained three times with CHCl₃ and removing the water azeotropically with methanol using the rotavap. Crystallization with ethanol/ether gave 262 mg (67%) of white crystalline 134.

FeCl₃ test for catechols: positive

mp = 160-162°C
$^1$H NMR (D$_2$O):

7.45-7.10 (m, 5H, Ar-H)
6.70 (s, 1H, Ar-H)
6.11 (s, 2H, Ar-H)
6.05 (s, 1H, Ar-H)
4.22 (br s, 2H, Ar-CH$_2$-N)
3.80-2.90 (m, 16H, 3 x Ar-0CH$_3$, CH, 3 x CH$_2$)

IR (KBr) cm$^{-1}$: 3220 (OH)

MS: 435 (M$^+$ - HCl), 254 (base), 181, 91

Analysis for C$_{26}$H$_{30}$N$_{14}$O$_5$Cl

Calculated: C, 66.16; H, 6.41; N, 2.97;
found: C, 66.07; H, 6.55; N, 2.76.

1-(3',4',5'-Trimethoxybenzyl)-2-benzyl-6,7-diacetyl-1,2,3,4-tetrahydroisoquinoline hydrochloride (135)

To 354 mg (0.750 mmol) of catechol 134 (before CHCl$_3$ washing) in 5 ml CHCl$_3$ was added 1.5 ml Et$_3$N and 110 mg
4-dimethylaminopyridine (DMAP) and 0.20 ml (2.120 mmol) acetic anhydride while cooling with ice-water. The mixture was allowed to warm up to RT and stirred overnight. The mixture was then washed twice with H₂O, saturated NaHCO₃, and H₂O. It was dried over MgSO₄, concentrated and purified by flash chromatography using 45% ethyl acetate in hexane as eluting solution. The HCl salt was prepared and crystallization using CHCl₃/ether gave 203 mg (49%) of white crystalline diacetate 135.

mp = 181-183°C

¹H NMR (CDCl₃, free base):
7.21 (s, 5H, Ar-H)
6.93 (s, 1H, Ar-H)
6.56 (s, 1H, Ar-H)
6.20 (s, 2H, Ar-H)
3.84 (s, 3H, Ar-OCH₃)
3.78 (s, 2H, N-CH₂-Ph)
3.73 (m, 6H, Ar-OCH₃)
3.30-2.61 (m, 7H, CH, 3 × CH₂)
2.27 (s, 3H, CH₃-C=O)
2.23 (s, 3H, CH₃-C=O)

IR (KBr) cm⁻¹: 1775, 1765 (C=O)

MS: 519 (M⁺ - HCl), 338 (base), 296, 53, 181, 91
Analysis for $C_{30}H_{34}NO_7Cl$

Calculated: C, 64.80; H, 6.16; N, 2.52;

found: C, 64.63; H, 6.10; N, 2.53.

1-(3',4',5'-Trimethoxybenzyl)-2-benzyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (134)

Method b)

A mixture of 54 mg (0.097 mmol) of the diacetate 135 in 3 ml methanol/concentrated HCl (50:50) was refluxed while stirring under argon for 2 h. The solvents were removed by rotavap. Methanol was added to the residue, removed by rotavap and this process repeated. Crystallization done with THF/ether (or ethanol/ether) gave 44 mg (96%) of catechol 125. This compound was identical with 134 prepared by Method a.
1-(3',4',5'-Trimethoxybenzyl)-2-chloroacetyl-6,7-dibenzyl-oxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (136)

To a mixture of 2.30 g (4.09 mmol) of amine salt 131 in 50 ml dry acetonitrile, 1.60 g (15.09 mmol) Na₂CO₃ was added, followed by addition of a solution of 1.91 g (11.17 mmol) chloroacetic anhydride [(ClCH₂CO)₂O] in 20 ml dry acetonitrile in dropwise manner. The mixture was then allowed to stir at RT overnight (20 h). The mixture was filtered and the filtrate concentrated under vacuum. The residue was redissolved in CHCl₃ and washed twice with 50 ml 10% Na₂CO₃. The organic layer was then dried over Na₂SO₄ and concentrated to give a yellow oil which turned solid. Purification of the solid by column chromatography using silica gel (particle size 0.063-0.2 mm) as packing and ethyl acetate/hexane (6:4 then 6.5:3.5) as eluting solution was carried out. The appropriate fraction were concentrated and crystallization using CH₂Cl₂/hexane gave 1.97 g (85%) of white crystalline amide.

mp = 124-125°C
$^1$H NMR (CDCl$_3$):

7.39-7.33 (m, 10H, Ar-H)
6.37 (s, 1H, Ar-H)
6.30 (s, 1H, Ar-H)
6.17 (s, 2H, Ar-H)
5.12, 5.10 (d, 4H, Ar-CH$_2$-O)
4.10 (s, 2H, O=CH$_2$-Cl)
3.83-2.56 (m, 16H, 3 x Ar-CH$_3$, CH, 3 x CH$_2$)

IR (KBr) cm$^{-1}$: 1640 (C=O)

MS: 420, 386, 181, 91 (base)

Analysis for C$_{35}$H$_{36}$NO$_6$Cl

Calculated: C, 69.82; H, 6.03; N, 2.33;

found: C, 69.71; H, 5.98; N, 2.25.
1-(3',4',5'-Trimethoxybenzyl-2-β-hydroxyethyl-6,7-dibenzyl-oxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (141)

A solution of 2.40 g (4.27 mmol) of the amine salt 131 in CHCl₃ was washed three times with saturated NaHCO₃ solution and once with H₂O to form the amine. The CHCl₃ solution was dried over MgSO₄, concentrated and redissolved in 80 ml ethanol. The solution was cooled down with ice-water and 100 ml ethylene oxide added. Stirring under CaCl₂ drying tube and at 0°C or below continued for 10 h. The mixture was then allowed to warm up to RT, and stirred overnight (10 h). Ethanol and excess ethylene oxide were removed by rotavap. The residue amine alcohol was redissolved in methanol and HCl gas bubbled in to make the HCl salt. The methanol and excess HCl were removed by rotavap. Crystallization using MeOH/ether was done to give 1.97 g (76%) of the amine alcohol salt 141.

mp = 98-100°C

¹H NMR (CDCl₃, free base):
7.52-7.29 (m, 10H, Ar-H)
6.68 (s, 1H, Ar-H)
6.39 (s, 1H, Ar-H)
6.32 (s, 2H, Ar-H)
5.12 (s, 2H, Ar-CH2-O)
4.98 (s, 2H, Ar-CH2-O)
3.82 (s, 9H, 3 x Ar-OC6H3)
3.75-2.45 (m, 7H, CH, 3 x CH2)

IR (KBr) cm⁻¹: 3640 (OH), 3230 (OH)
MS: 569 (M⁺ - HCl), 388, 181, 91 (base)

Analysis for C35H40NO6Cl • H2O
Calculated: C, 67.35; H, 6.78, N, 2.24;
found: C, 67.57; H, 6.61; N, 2.26.

\[
\text{HO} \quad \text{HO} \quad \text{HCICH} \\
\text{N} \quad \text{Cl} \\
\text{CH2} \quad \text{HCl} \\
\text{CH3O} \quad \text{OCH3} \\
\text{OCH3} \\
\text{CH3O} \quad \text{OCH3}
\]

Hydrogenation of 970 mg (1.60 mmol) of amine alcohol salt 141, in 50 ml dry ethanol with 86 mg 10% Pd/C as
catalyst was done at 45 psi for 16 h. The catalyst was fil­
tered off, the filtrate concentrated to a small volume and
passed over Celite. The remaining ethanol was removed under
vacuum. Attempts to crystallize the oil obtained in several
solvent systems were not successful. The oil was then
placed under high vacuum to give 617 mg (91%) of a yellow
fluffy solid.

FeCl₃ test for catechols: positive

An analytical sample was prepared by dissolving 226 mg of
the catechol above in water, washing the water solution
three times with CHCl₃ and azeotroping the water off with
methanol using rotavap. The oil residue was placed under
vacuum to give 0.197 mg (87%) of a yellow-white solid.

mp = 100-104°C

¹H NMR (D₂O):

6.64 (s, 1H, Ar-H)
6.27 (s, 2H, Ar-H)
5.86 (s, 1H, Ar-H)
3.86-3.74 (t, 2H, -CH₂-OH)
3.62 (s, 3H, Ar-OCH₃)
3.61 (s, 6H, 2 × Ar-OCH₃)
3.50-2.81 (m, 9H, CH, 4 × CH₂)

IR (KBr) cm⁻¹: 3200 (br, OH)

MS: 208 (base), 181
Analysis for $\text{C}_{21}\text{H}_{28}\text{NO}_{6}\text{Cl} \cdot \text{H}_2\text{O}$

Calculated: C, 56.82; H, 6.81; N, 3.16;
found: C, 56.93; H, 6.65; N, 3.20.

1-(3',4',5'-Trimethoxybenzyl)-β-hydroxyethyl-6,7-dihydroxy-
1,2,3,4-tetrahydroisoquinoline oxalate (144)

A solution of 1.40 g (2.31 mmol) of amine salt 141 in
$\text{CH}_2\text{Cl}_2$ was washed three times with a saturated $\text{NaHCO}_3$ solution, twice with $\text{H}_2\text{O}$ and dried over $\text{MgSO}_4$. To this amine in
methanol was added 280 mg (2.21 mmol) oxalic acid in metha-
nol at RT. Addition of ether gave 958 mg (66%) of a white
crystalline oxalate salt.

mp = 99-101°C

MS: 569 ($\text{M}^+$ - oxalate), 388, 181, 91, base

A mixture of 418 mg (0.664 mmol) of the oxalate salt in
30 ml ethanol and 109 mg 10% Pd/C was hydrogenated at 40 psi
for 10 h. Filtration of the mixture was followed by removal
of solvent under vacuum. The residue was redissolved in a small amount of methanol filtered over Celite and crystallized in MeOH/ether to give 198 mg (68%) of the oxalate catechol.

FeCl₃ test for catechols: positive

mp = 217-218°C

Analysis for C₂₁H₂₇NO₆ • 1/2 oxalate • 1/4 H₂O

Calculated: C, 60.20; H, 6.54; N, 3.19;
found: C, 60.01; H, 6.64; N, 3.07.

1-(3',4',5'-Trimethoxybenzyl)-2-β-chloroethyl-6,7-cyclic sulfite-1,2,3,4-tetrahydroisoquinoline hydrochloride (145)

While cooling a solution of 332 mg (0.780 mmol) of the amine alcohol 143 in 15 ml dry tetrahydrofuran under argon with ice water, 0.3 ml (4.11 mmol) thionyl chloride was added to the mixture. Stirring with cooling was continued for 2 h after which the mixture was allowed to warm up to RT and
stirred overnight (18 h). A white compound crystallized out of the solution. It was filtered under suction and washed with ether to give 334 mg (87%) of compound 145.

FeCl₃ test for catechols: positive

mp = 184-186°C

¹H NMR (D₂O):

  6.67 (s, 1H, Ar-H)
  6.33 (s, 2H, Ar-H)
  5.95 (s, 1H, Ar-H)
  3.90-2.85 (m, 20H, 3 x Ar-CH₃, CH, 5 x CH₂)

MS: 418, 72 (base), 181

Analysis for C₂₁H₂₅NO₆Cl₂S

Calculated:  C, 51.43; H, 5.14; N, 2.86;
      found:  C, 51.22; H, 5.13; N, 2.83.
l-(3',4',5',-Trimethoxybenzyl)2-β-chloroethyl-6,7-di-
hydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (138)

A solution of 200 mg (0.408 mmol) of compound 145 in
10 ml methanol/water (50:50 mixture) was stirred under argon
at RT for 4 days. The methanol was removed by rotavap and
the water removed by freeze-drying to give 180 mg (99%) of
compound 138.

mp = 105-110°C

1H NMR (D2O):

6.65 (s, 1H, Ar-H)
6.35-6.30 (d, 2H, Ar-H)
5.91 (s, 1H, Ar-H)
3.87-2.86 (m, 20H, 3 x Ar-0CH3, CH, 5 x CH2)

IR (KBr) cm⁻¹: 3370, 3190, (br, OH)

MS: 228, 226 (base), 181

Analysis for C21H27NO5Cl2 • 3/4 H2O

Calculated:  C, 55.09; H, 6.27; N, 3.06;

found:  C, 54.98; H, 6.36; N, 3.20.
The amine salt 147 was prepared from amide 129 in a similar manner as amine salt 133 but for the following modifications:

\[
\begin{align*}
\text{Amide} & = 4.00 \text{ g} \ (7.39 \text{ mmol}) \\
\text{CH}_3\text{CN} & = 80 \text{ ml} \\
\text{POCl}_3 & = 2.5 \text{ ml} \ (26.82 \text{ mmol})
\end{align*}
\]

The mixture was refluxed for 3.25 h and worked up as before. Methylation of the imine was done in a similar manner as the benzylation but for these modifications:

\[
\begin{align*}
\text{Toluene} & = 50 \text{ ml} \\
\text{Methyl Iodide} & = 1.5 \text{ ml} \ (24.09 \text{ mmol}) \\
T & = 40^\circ\text{C} \\
\text{Reaction time} & = 10 \text{ h}
\end{align*}
\]

A yellow solid crystallized out of the solution during the reaction. The solution was allowed to cool to RT, some ether added and the mixture cooled with ice-water. The
yellow crystals were filtered and washed with ether to give 3.28 g (63%) of the imine salt.
mp = 192-194°C.

Reduction of the imine salt also was done as before.

Imine salt \( \text{146} \) = 2.60 g (3.71 mmol)
ethanol = 70 ml

\[ \text{NaBH}_4 = 2.60 \text{ g (68.73 mmol)} \]

Reaction time = 8 h

The colour of the mixture changed from yellow to colourless during the reaction. Ethanol was removed by rotavap and the residue redissolved in \( \text{CHCl}_3/10\% \text{ NaOH} \). The layers were separated and the organic layer washed once with 10% NaOH, twice with \( \text{H}_2\text{O} \) and dried over \( \text{MgSO}_4 \). HCl salt of the amine was made but could not be crystallized. It was then put on a pump to give 1.97 g (92%) of a white fluffy solid.

mp = 67-72°C

\(^1\text{H NMR (CDCl}_3, \text{ free base)}

\[
7.46-7.32 \text{ (m, 10H, Ar-H)} \\
6.67 \text{ (s, 1H, Ar-H)} \\
6.29 \text{ (s, 2H, Ar-H)} \\
6.24 \text{ (s, 1H, Ar-H)} \\
5.10 \text{ (s, 2H, Ar-CH}_2\text{-O)} \\
4.87,4.86 \text{ (d, 2H, Ar-CH}_2\text{-O)} \\
3.82 \text{ (s, 3H, Ar-CH}_3\text{)}
\]
3.76 (s, 6H, Ar-OCH₃)
3.70-2.58 (m, 7H, CH, 3 × CH₂)
2.53 (s, 3H, N-CH₃)

MS: 539 (M⁺ - HCl), 358 (base), 181, 91

Analysis for C₃₄H₃₈NO₅Cl
Calculated: C, 70.88, H, 6.65; N, 2.43;
found: C, 70.67; H, 6.85; N, 2.35.

1-(3',4',5'-Trimethoxybenzyl)-2-methyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (148)

Method a)

Hydrogenation of 115 mg (0.200 mmol) of amine salt 147 in 20 ml EtOH using 18 mg 10% Pd/C as catalyst was done at 40 psi for 16 h. Filtration was followed by removing the ethanol and crystallizing in MeOH/ether to give 48 mg (61%) of catechol 148 as a white-light brown crystalline material. FeCl₃ test for catechols: positive

mp = 219-221°C
Method b)

A mixture of 333 mg (0.578 mmol) of amine salt 147, 10 ml MeOH and 10 ml concentrated HCl was refluxed for 30 h. Methanol and HCl solution were then removed by rotavap. The residue was redissolved in MeOH and the MeOH removed by rotavap. This procedure was repeated twice and gave a yellow solid. Crystallization in MeOH/ether gave 154 mg (67%) of catechol 148 as a white crystalline material.

FeCl₃ test for catechols: positive

mp = 222-224°C

¹H NMR (D₂O):

6.66 (s, 1H, Ar-H)
6.27 (s, 2H, Ar-H)
5.96 (s, 1H, Ar-H)
3.64 (s, 3H, Ar-OCH₃)
3.62 (s, 6H, Ar-OCH₃)
3.50-2.90 (m, 7H, CH, 3 × CH₂)
2.82 (s, 3H, N-CH₃)

IR (KBr) cm⁻¹: 3455 (OH)

MS: 359 (M⁺ - HCl), 181, 178 (base)

Analysis for C₂₀H₂₆NO₅Cl

Calculated:  C, 60.68; H, 6.62; N, 3.54;
found:  C, 60.39; H, 6.79; N, 3.37.
A solution of 2.15 g (3.83 mmol) of the amine salt 131 in CHCl₃ was extracted four times with a saturated NaHCO₃ solution. The CHCl₃ solution was then washed twice with water, dried over MgSO₄ and concentrated. The residue obtained was redissolved in 20 ml CH₂Cl₂, cooled with ice-water followed by addition of 8 ml Et₃N, 0.584 g (4.78 mmol) DMAP and 0.5 ml (5.30 mmol) acetic anhydride. The solution was then allowed to warm up to RT gradually and stirred overnight (10 h). Work-up consisted of washing the CH₂Cl₂ solution with 5% HCl, once with water, twice with saturated NaHCO₃ solution and twice with H₂O. The CH₂Cl₂ solution was then dried over MgSO₄, concentrated and crystallized from CH₂Cl₂/ether to give 1.42 g (65%) of amide 149.

mp = 126-127°C

¹H NMR (CDCl₃):

7.46-7.26 (m, 10H, Ar-H)
6.32 (s, 1H, Ar-H)
6.28 (s, 1H, Ar-H)
6.19 (s, 2H, Ar-H)
5.14, 5.11 (d, 4H, Ar-CH₂-0)
3.82-2.56 (m, 16H, 3 × Ar-OCH₃, CH, 3x CH₂)
2.14 (s, 3H, O=C-CH₃)

IR (KBr) cm⁻¹: 1640 (C=O)
MS: 567 (M⁺), 386 (base), 296, 181, 91

Analysis for C₃₅H₃₇NO₆
Calculated: C, 74.05; H, 6.57; N, 2.47;
found: C, 74.20; H, 6.61; N, 2.40.

1-(3',4',5'-Trimethoxybenzyl)-2-ethyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (150)

To a solution of 577 mg (1.02 mmol) of amide 149 in 30 ml THF was added 5 ml 0.98 M BH₃ in THF. The mixture was refluxed for 12 h, cooled with ice-water, ether saturated with HCl gas was added followed by bubbling HCl gas into
this mixture. The mixture was then concentrated and the residue redissolved in CH$_2$Cl$_2$, washed twice with H$_2$O and dried over Na$_2$SO$_4$. HCl gas was then bubbled in to give the amine salt as an oil. To half of this material was added 5 ml MeOH and 5 ml concentrated HCl. The mixture was then refluxed for 48 h, solvents removed and the mixture put under vacuum overnight to give 176 mg (84%) of a white fluffy solid.

FeCl$_3$ test for catechols: positive

$^1$H NMR (D$_2$O):

- 6.64 (s, 1H, Ar-H)
- 6.25 (s, 2H, Ar-H)
- 5.90 (s, 1H, Ar-H)
- 3.62 (s, 3H, Ar-OCH$_3$)
- 3.60 (s, 6H, Ar-OCH$_3$)
- 3.50-2.80 (m, 9H, CH, 4 × CH$_2$)
- 1.30-1.15 (t, 3H, CH$_3$)

IR (KBr) cm$^{-1}$: 3200 (br, OH)
2-(2'-Fluoro-3',4'-dibenzylxyloxyphenyl)ethylamine hydrochloride (151)

A solution of 0.95 g (2.74 mmol) of 2-Fluoro-3,4-dibenzylxyloxyphenyl acetonitrile in 10 ml dry THF was added slowly to 10 ml 0.98 M BH₃ in THF with ice-water bath cooling. The resultant solution was refluxed for 1.5 h and cooled with ice-water. Slow addition of 10 ml MeOH was followed by refluxing the mixture for 30 min and concentrating. The residue was redissolved in MeOH, concentrated and redissolved in MeOH. HCl gas was bubbled into this mixture, concentrated and this step was repeated. The residue was dissolved in 90 ml H₂O containing 2 ml 10% HCl, washed twice with ether, basified with 10% NaOH and extracted with ether. The aqueous solution was partially saturated with NaCl and extracted twice with ether. The ether extracts were combined, dried over MgSO₄ and concentrated. The residue was redissolved in CHCl₃, HCl salt made and the amine salt crystallized out in CHCl₃/ether to give 0.63 g (59%) of a white crystalline material.
mp = 111-113°C
IR (KBr) cm⁻¹: 3400 (broad, NH)

¹H NMR (CDCl₃, free base)
  7.45-7.25 (m, 10H, Ar-H)
  6.90-6.60 (m, 2H, Ar-H meta & para to F)
  5.10 (s, 4H, Ar-CH₂-O)
  2.90-2.60 (m, 4H, 2 × CH₂-O)
  1.26 (s, 2H, NH₂)

MS: 351 (M⁺ - HCl), 322, 91 (base)

Analysis for C₂₂H₂₃N0₂FC₁
  Calculated: C, 68.13; H, 5.98; N, 3.61; F, 4.90;
  found: C, 67.91; H, 6.15; N, 3.50; F, 4.86.

**N-(2-Fluoro-3,4,-dibenzyloxyphenylethyl)-3',4',5'-tri-
methoxyphenylacetamide (153)**

Synthesis of this amide was done as in the synthesis of
amide 129 above but for the following modifications and cor-
responding scaling down of all solutions: Synthesis of this amide was done as in the synthesis of amide 129 above but for the following modifications and corresponding scaling down of all solutions:

Fluorophenethylamine • HCl (151) = 0.553 g (1.426 mmol)
Trimethoxyphenylacetic acid (128) = 0.348 g (1.538 mmol)
toluene = 15 ml
t = 48 h

The fluoroamide 153 was crystallized from icluene to give 247 mg (31% yield) of a white crystalline material.

mp = 109-111°C

$^1$H NMR (CDCl$_3$):

7.54-7.29 (m, 10H, Ar-H)
6.62-6.57 (m, 2H, Ar-H)
6.39 (s, 2H, Ar-H)
5.54-5.35 (br, 1H, NH)
5.10-5.07 (d, 4H, 2 × Ar-CH$_2$-0)
3.86 (s, 3H, Ar-OCH$_3$)
3.80 (s, 6H, 2 × Ar-OCH$_3$)
3.56-3.32 (m, 4H, Ar-CH$_2$-C)
2.79-2.64 (t, 2H, CH$_2$-N)

IR (KBr) cm$^{-1}$: 3280 (NH), 1635 (C=O)

Analysis for C$_{33}$H$_{34}$NO$_6$F

Calculated: C, 70.83; H, 6.12; N, 2.50; F, 3.40;
found: C, 70.55; H, 6.27; N, 2.33; F, 3.31.
A solution of 1.96 g (10.04 mmol) of nitrile 53 in 20 ml THF was added slowly to 20 ml 0.98 M BH₃ in THF with ice-water bath cooling. The resultant mixture was refluxed for 1.5 h, cooled in an ice-water bath and 250 ml MeOH was added slowly. The mixture was refluxed for 0.5 h and concentrated. Methanol was then added to the residue, removed under vacuum and this step repeated twice. The residue was redissolved in 20 ml MeOH and HBr bubbled into this solution while stirring and until litmus paper showed the solution to be acidic. Removal of the MeOH, redissolving in MeOH and filtering were followed by crystallization using MeOH/ether to give 2.24 g (80%) of a white crystalline material.

mp = 171-173°C (lit. 174-177°C)

IR (KBr) cm⁻¹: 3050 (⁺NH₃)

¹H NMR (CDCl₃, free base):

6.93-6.57 (m, 2H, Ar-H)
3.92-3.91 (d, 3H, Ar-OCH₃ ortho to F)
3.86 (s, 3H, Ar-OCH₃ meta to F)
3.02-2.65 (m, 4H, 2 × CH₂)
1.50 (br 2H, NH₂)

2-(2'-Fluoro-3',4'-dihydroxyphenyl)ethylamine hydrobromide
[2-Fluorodopamine hydrobromide, (157)]

A mixture of 327 mg (1.167 mmol) of the amine salt 156 in 10 ml 48% HBr was heated at 140°C for 7 h under argon. Excess HBr was removed by rotavap. Methanol was added to the residue and then removed under vacuum. This was repeated and the residue obtained was put on pump overnight to give 280 mg (95%) of a brown material. Catechol test for catechols: positive

mp = 160-162°C (lit. mp = 158-160°C)

¹H NMR (D₂O):
6.58-6.53 (m, 2H, Ar-H)
3.20-2.71 (m, 4H, 2 × CH₂)

IR (KBr) cm⁻¹: 3520 (OH), 3360 (OH), 3120-3040 (⁺NH₃)
**BIOLOGY**

**β-Adrenergic Studies**

Male albino Hartley guinea pigs (weighing 400 to 600 g) were employed in all experiments. The isolation and procedures for testing of each compound in isolated guinea pig atria and trachea were identical with those described by Miller and Feller. Responses were recorded on a Grass (Model 7) polygraph via FT-03 force displacement transducers. Each drug concentration was added only after the effects of the previous concentration reached a maximum and remained constant. The final maximum concentration was considered to be that response at which further addition of a higher concentration of the testing compound did not increase the effect. Responses for agonists were expressed as \( pD_2 \) values \(-\log [ED_{50}] \) and were calculated directly from graphical plots of % maximal response versus log molar drug concentration.

**Platelet Antiaggregatory Activities**

**Materials:**

\(^{14}\)C serotonin (58 mCi/m mole) and Formula 963 were purchased from New England Nuclear (Boston, MA). Albumin,
apyrase and TRIS base were purchased from the Sigma Chemical Co. (St. Louis, MO). U46619 was obtained from Upjohn Diagnostics, Inc. (Kalamazoo, MI). Trimetoquinol isomers were kindly provided by Dr. Yoshio Iwasawa (Tanabe Seiyaku Co., Ltd., Saitama, Japan).

Methods:

The methods used for the pharmacological evaluations of the drugs in human platelets are:
(a) preparation of washed platelet suspensions;
(b) measurement of platelet aggregation;
(c) measurement of the secretion of \[^{14}\text{C}]\text{serotonin};
(d) determination of inhibitory concentration - 50 (IC\textsubscript{50}) values

a) Preparation of washed human platelet suspensions:

Blood was taken by venipuncture from normal healthy donors who had been free of aspirin-containing medication for at least 14 days. Whole venous blood was mixed with acid-citrate dextrose (ACD) anticoagulant (6:1, v/v) and centrifuged at 120 g for 15 min at room temperature to obtain platelet-rich plasma (PRP). PRP was centrifuged at 1100 g for 3 min and the resulting platelet pellet was resuspended in 50 mM TRIS-HCl (pH = 7.5) buffer solution containing 20 mM EDTA. Apyrase (EC3.6.1.5),
(34 μg/ml) was also added to this suspension to prevent accumulation of ADP. The suspension was centrifuged at 1100 g for 3 min for first wash. The washing procedure was repeated three times and the final platelet pellet was resuspended in a modified Tyrode's solution (pH = 7.4) containing calcium. Platelet counts were adjusted to $3 \times 10^8$ platelets/ml to perform functional studies.

b) Measurement of platelet aggregation:

Platelet aggregation studies were performed according to the turbidometric method of Born, as modified by Mustard et al., using a Payton aggregometer. Incubation of 0.45 ml washed human platelets with 0.05 ml of vehicle or drug (total volume = 0.5 ml) was done for 3 min at 37°C prior to the initiation of aggregation with U46619. This time period also served as the incubation interval for the TMQ isomers and analogs. In all experiments, the minimum concentration of U46619 (0.8-2.0 μM) which caused maximal irreversible aggregation within each preparation was used. Aggregation was monitored for at least 2 min after the addition of U46619 and data were expressed as a percentage inhibition of the maximal light transmittance to U46619 in the presence of varying drug concentrations.
Measurement of the secretion of $[^{14}\text{C}]$serotonin:

Secretion of serotonin from dense granules was measured by monitoring the release of radioactivity from the same samples used for measurement of platelet aggregation. Release of serotonin from platelets was measured by centrifugation of samples at 10,000 g for 30 sec in a microfuge and determining the radioactivity present in an aliquot (100 μL) of the supernatant. Total radioactivity was measured after lysis of platelets with Protosol solubilizer (1 ml) and the centrifugation. Liquid scintillation spectrometry using a Beckman Liquid Scintillation counter (Model LS 6800, Palo Alto, CA) and an emulsion-type scintillation mixture (Formula 963) were used to determine the amount of the $^{14}\text{C}$ in supernatants of lysed or non-lysed samples.

Secretion data was calculated as the net increase of serotonin released into the supernatant by U46619 and expressed as a percentage of the total radioactivity in platelets. The effect of compounds on serotonin release were expressed as the percentage inhibition of the maximum release by U46619 and plotted against log molar concentrations of each agent.


**d) Determination of inhibitory concentration-50 (IC\textsubscript{50}) values:**

IC\textsubscript{50} values for each drug were estimated from graphical plots of % Inhibition versus log molar concentration of each drug, and were defined as the concentration required to produce a 50% inhibition of the maximal aggregatory or secretory response to U46619. Data were expressed as the mean ± standard error of the mean (S.E.) of results obtained from 3 or more preparations.
SUMMARY

Trimetoquinol, TMQ, is a potent β-adrenergic agonist and an inhibitor of platelet aggregation. This study was directed at the synthesis and pharmacological evaluation of several N-substituted and fluorinated analogs of TMQ. Knowledge gained from this study include the following:

a) Synthesis of several N-substituted TMQ analogs where the substituent included methyl, ethyl, benzyl, β-hydroxy ethyl and β-chloroethyl groups.

b) Selective cleavage of O-benzyl groups in the presence of an N-benzyl using HCl.

c) Formation of a cyclic sulfite ester from the reaction of a catechol with SOCl₂.

d) Synthesis of a fluorinated dibenzyloxyphenethylamine which could serve as a versatile intermediate in the synthesis of fluorinated phenethylamines.

e) The bigger the N-substituent, the lower β-adrenergic activity but the higher the inhibition of platelet aggregatory activity. However, TMQ remained the most potent in the series.

f) In the β-adrenoceptor systems, β₂ was better able to tolerate N-bulky substituents than β₁.
Appendix A

SELECTED SPECTRA FROM PART I
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