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SYNTHESIS AND BIOLOGICAL STUDIES 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

Jane Chang, B.S., M.S.

* * * * *

The Ohio State University
1982

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FIELDS OF STUDY

Major Field: Medicinal Chemistry

-iii-
TABLE OF CONTENTS

ACKNOWLEDGEMENTS ........................................... ii
VITA ............................................................. iii
LIST OF TABLES ................................................ vi
LIST OF FIGURES ............................................... vii

Chapter

I. INTRODUCTION ............................................... 1

   Biology.................................................... 1
   Beta Receptors and Beta Agonists ............... 1
   Platelet Aggregation Pathways .......... 7
   Chemistry ............................................... 12
      Benzylisoquinolines .................. 12
      Phenethylisoquinoline ......... 17
      2- and 3- Tetrahydrobenzazepines .... 18
      Structure Activity Relationships
         of Trimetoquinol .................. 22

II. STATEMENT OF PROBLEM AND OBJECTS .................. 26

III. RESULTS AND DISCUSSION ............................... 29

   Synthetic Approach ................................... 29
      The Alpha-Benzylc Substituted
         Trimetoquinol Analogs ............ 29
      The 1-Naphthyl Substituted Trimetoquinol
         Analogs .......................... 38
      The 1-Phenethyl Analog of Trimetoquinol 40
      The 2-Tetrahydrobenzazepine Analog of
         Trimetoquinol .................... 42
      The 3-Tetrahydrobenzazepine Analogs of
         Trimetoquinol .................... 48
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Biological Results and Discussion</td>
<td>64</td>
</tr>
<tr>
<td>Evaluation of Compounds in Beta Adrenergic Tissues</td>
<td>64</td>
</tr>
<tr>
<td>Evaluation of Compounds in Human Platelet Preparations</td>
<td>79</td>
</tr>
<tr>
<td>Prostaglandin Dependent Pathway</td>
<td>79</td>
</tr>
<tr>
<td>Prostaglandin Independent Pathway</td>
<td>80</td>
</tr>
<tr>
<td>Biochemical Consequences of Phospholipase C Induced Aggregation</td>
<td>82</td>
</tr>
<tr>
<td>IV. EXPERIMENTAL</td>
<td>84</td>
</tr>
<tr>
<td>Synthetic Methods</td>
<td>84</td>
</tr>
<tr>
<td>Biological Methods</td>
<td>168</td>
</tr>
<tr>
<td>SUMMARY</td>
<td>170</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>172</td>
</tr>
</tbody>
</table>
LIST OF TABLES

Table                                                                 
                                                                 page
1. Effect of compound 65 on the dose response relationship of (-)-isoproterenol on isolated tracheal smooth muscle and right auricular preparations....... 77
2. The inhibitory activity of the trimetoquinol isomers and analogs against aggregation induced by U46619 (2μM) .......................................................... 79
3. The inhibitory activity of the trimetoquinol isomers and analogs against aggregation induced by phospholipase C (0.05 U/ml) ............................. 81
4. The inhibitory activity of the trimetoquinol isomers and analogs against aggregation induced by thrombin (0.03 U/ml) ................................. 83
LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Proposed platelet aggregation pathways</td>
<td>11</td>
</tr>
<tr>
<td>2. Dose reponse curve for (+) trimetoquinol (12) and the dimethyl analog (58) on the relaxation of guinea pig tracheal smooth muscle</td>
<td>65</td>
</tr>
<tr>
<td>3. Dose response curve for (+) trimetoquinol (12) and the dimethyl analog (58) on the spontaneously beating guinea pig right atrium</td>
<td>66</td>
</tr>
<tr>
<td>4. Dose reponse curve for the erythro- (59) and three- (60) monoisopropyl trimetoquinol analog on the relaxation of guinea pig tracheal smooth muscle</td>
<td>68</td>
</tr>
<tr>
<td>5. Dose reponse curve for the erythro- (59) and three- (60) monoisopropyl trimetoquinol analog on the spontaneously beating guinea pig right atrium</td>
<td>69</td>
</tr>
<tr>
<td>6. Dose response curve for trimetoquinol analogs 61 and 62 on the relaxation of guinea pig tracheal smooth muscle</td>
<td>71</td>
</tr>
<tr>
<td>7. Dose response curve for trimetoquinol analogs 61 and 62 on the spontaneously beating guinea pig right atrium</td>
<td>72</td>
</tr>
<tr>
<td>8. Effect of trimetoquinol analog 61 on the dose response curve of (-)-isoproterenol-d-bitartrate on the spontaneously beating guinea pig right auricle</td>
<td>73</td>
</tr>
<tr>
<td>9. Dose response curve for the tetrahydrobenzazepine analogs of trimetoquinol 64, 65 and 66 on the relaxation of guinea pig tracheal smooth muscle</td>
<td>75</td>
</tr>
<tr>
<td>10. Dose response curve for the tetrahydrobenzazepine analogs of trimetoquinol 64, 65 on the spontaneously beating guinea pig right atrium</td>
<td>76</td>
</tr>
</tbody>
</table>
Chapter I
INTRODUCTION

BIOLOGY
Beta Receptors and Beta Agonists

The peripheral nervous system is divided into two parts: the somatic nervous system which controls the activity of voluntary muscles and the autonomic nervous system which controls the activity of involuntary organs. In the latter, the adrenergic nervous system and cholinergic nervous system are the main segments. Norepinephrine (1) is the neurotransmitter of adrenergic nervous system, while acetylcholine (2) is the neurotransmitter of cholinergic nervous system.

In 1948, Ahlquist\(^1\) first proposed the concept of alpha and beta receptors. Based on the observation that in a series of six catecholamines, there were two distinct sequences of activities in a variety of smooth and cardiac muscle preparations. For alpha receptors, the order of activities is
(-)-epinephrine (3) > (+)-epinephrine (3) > norepinephrine (1) > alpha-methylnorepinephrine (4) > alpha-methylepinephrine (5) > isoproterenol (6), while for beta-receptors, the order is isoproterenol (6) > (-)-epinephrine (3) > alpha-methylepinephrine (5) > (+)-epinephrine (3) > alpha-methylnorepinephrine (4) > norepinephrine (1). In 1967, Lands et al. 2,3, further postulated that there are two types of beta receptors: beta-1 and beta-2 (Scheme 1).

Scheme 1

Peripheral Nervous System

<table>
<thead>
<tr>
<th>Autonomic Nervous System</th>
<th>Somatic Nervous System</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenergic nervous system (norepinephrine)</td>
<td>Cholinergic nervous system (acetylcholine)</td>
</tr>
<tr>
<td>Alpha receptors</td>
<td>Beta receptors</td>
</tr>
<tr>
<td>Beta-1 receptors</td>
<td>Beta-2 receptors</td>
</tr>
</tbody>
</table>
Beta receptors differ in the relative potencies for isoproterenol (6), epinephrine (3), and norepinephrine\(^1\). For beta-1 receptors in the gut, atria, heart, and adipose tissue, the order of activities is isoproterenol (6) > norepinephrine (1) > epinephrine (3). For the beta-2 receptors in aorta and trachea, the order is isoproterenol (6) > epinephrine (3) >> norépinephrine (1). For both beta-1 and beta-2 receptors, the distinction by agonists is enhanced by the action of a number of antagonists, while practolol (7) is described as a selective beta-1 antagonist, butoxamine (8) is a selective beta-2 antagonist and propranolol (9) is a nonselective beta antagonist\(^4,5,6\).

The beta-receptor is thought to be a membrane component and is located on the outer surface. It has been shown that a catecholamine covalently attached to glass beads\(^7,8\) can activate beta-receptors while intracellularly applied norépinephrine can not\(^9\). The beta-receptor and adenylyl cyclase are intimately associated. Although the detailed organization of adenylyl cyclase was not well defined, the concept of the ubiquitous cAMP as a "secondary messenger" has been well accepted. cAMP changes and biological events correlate both qualitatively and quantitatively\(^10,11\). Catecholamine stimulation of adenylyl cyclase is completely antagonized by beta-antagonists but not by alpha-antagonists\(^12-15\). Furthermore, the marked stereoselectivities of beta-agonist and antagonists are also observed with adenylyl cyclase activity.
In other words, the R-enantiomers of catecholamines related to norepinephrine are more active than the S-enantiomers\textsuperscript{16,17,18} in activating adrenergic receptors.
The mechanism associated with the antiasthmatic activity of beta-2 agonists is due to the stimulation of adenyl cyclase and the intracellular formation of cAMP which further produces the relaxation of lung smooth muscle\textsuperscript{19,20} and inhibition of the release of bronchoconstrictive agents such as histamine, SRS-A and prostaglandins from mast cells in allergic sensitized lung tissue\textsuperscript{21}.

A number of compounds have been studied for the selective beta-2 adrenergic activity. Norepinephrine (1) and epinephrine (3) stimulate both alpha and beta adrenergic receptors to about the same degree\textsuperscript{22}. Isoproterenol (6) is the most active of the adrenergic drugs which act almost exclusively on beta receptors by virtue of the N-alkyl substitution. It was first studied by Konzett\textsuperscript{23} in 1940 and has been used therapeutically to treat respiratory disorders and also as a cardiac stimulant. It stimulates both beta-1 and beta-2 adrenergic receptors. The stimulation of myocardium at beta-1 receptors may lead to undesirable tachycardia, increase in cardio output and an elevation in blood pres-
Sure\textsuperscript{24,25}. Metaproterenol (10) is an analog of isoproterenol in which the catechol ring system has been replaced by a resorcinol ring system. This change results in a compound that is no longer susceptible to metabolism by COMT and provides a longer duration of action (4 hours). Some selectivity towards beta-2 adrenergic receptors has been observed with metaproterenol but the activity is 10 to 40 times lower than isoproterenol\textsuperscript{26,27}. Terbutaline (11), which has a t-butyl substitution at the nitrogen, shows beta-2 selectivity\textsuperscript{28}. It is a potent orally active agent with a duration of action up to 7 hours\textsuperscript{22}. However, it can also stimulate the beta-receptors in skeletal muscles and produce tremors\textsuperscript{29,30}.
Trimetoquinol (12), 1-(3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, can be considered as a catecholamine fused into a tetrahydroisoquinoline ring system. It is a potent stimulant of both beta-1 and beta-2 adrenergic receptors. For pharmacological activity on beta-receptors, it has been found that S(-)-trimetoquinol was about twice as active as the racemate. The R(+) isomer of trimetoquinol had only weak beta activity and did not antagonize the activity of the S(-) isomer. In addition to beta adrenergic activities, trimetoquinol has been shown to have potent antiaggregatory properties in human platelet preparations. Very interestingly, the antiaggregatory action is mediated primarily by the R(+) trimetoquinol. This stereo-selectivity, as initially demonstrated by Dalton and others, suggested that the antiaggregatory activity by trimetoquinol was mediated by a mechanism dissociated from beta adrenergic receptors.

Platelet Aggregation Pathways

Platelet aggregation is stimulated by a number of substances such as collagen, thrombin, ADP, epinephrine, and thromboxane A2. All of these stimuli induce shape change of platelets and facilitate the aggregation of platelets to each other. After a short lag time of collagen stimulated aggregation, a number of substances such as ADP, serotonin, and calcium are released from storage granules within platelets.
There are four proposed pathways for platelet aggregation (Figure 1):

(a) The ADP pathway: ADP itself can stimulate platelet aggregation, but its mechanism remains uncertain. Although it has been shown that binding of ADP to the platelet surface exposed the masked fibrinogen receptors and thus fibrinogen can crosslink platelets together.

(b) The prostaglandin pathway: In studying ADP, epinephrine or collagen induced aggregation, a biphasic response is observed. The second phase of aggregation is due to the stimulation and release of arachidonic acid from platelet membrane phospholipids by activating phospholipase A2 or phospholipase c-diglyceride lipase sequence. Released arachidonic acid is converted by cyclooxygenase to prostaglandin endoperoxides \( \text{PGG}_2 \) and \( \text{PGH}_2 \), which in turn is rapidly converted by thromboxane synthetase to thromboxane A2. Prostaglandin endoperoxides have little or no platelet aggregatory activity while thromboxane A2 is a potent platelet aggregating agent, which promotes further platelet aggregation and secretion as does ADP.
(c) The platelet activating factor (PAF) pathway: Platelet activating factor, 1-O-alkyl — 2-acetyl — glyceryl 3-phosphorylcholine, PAF-acether\textsuperscript{52}, is a substance released from platelets by calcium ionophore A23187, collagen, thrombin or immune stimulation. In the presence of nonsteroidal anti-inflammatory drugs, which inhibit the synthesis of prostaglandins, and in the presence of creatine phosphate and creatine phosphokinase which scavenge the ADP, PAF-acether can still induce platelet aggregation\textsuperscript{53}. Therefore, PAF-acether indeed account for a third pathway of aggregation.

d) The phospholipase C pathway: Thrombin, a proteolytic enzyme can stimulate not only the prostaglandin pathway of platelet aggregation, but also stimulate a nonsteroidal anti-inflammatory drug and prostaglandin independent platelet aggregation\textsuperscript{54,55}. This action is not inhibited by ATP, an inhibitor of ADP induced aggregation\textsuperscript{56}. Recent studies indicated that thrombin stimulates a phosphatidylinositol specific phospholipase C in platelets\textsuperscript{57,58}. This enzyme converts the breakdown of phosphatidylinositol to diacylgly-
cerol which is further phosphorylated to form phosphatidic acid\(^{59}\). The turnover of phosphatidylinositol to diacylglyceride and then to phosphatidic acid has been linked to intracellular calcium mobilization which then produces platelet aggregation\(^{60,61}\).

R(+)–Trimetoquinol was shown to stereoselectively inhibit platelet aggregation by ADP, collagen, AA, TXA\(_2\) as mentioned earlier. The mechanism of this antiaggregatory activity has been shown to be as a competitive inhibitor of thromboxane A2 at thromboxane A2 receptors\(^{62}\).

Other inducers of platelet activation mediated their effect by a pathway independent of prostaglandin biosynthesis. Recently, it has been shown that a low dose of thrombin (0.03U/mL) or phospholipase C (from Clostridium perfringens) can cause aggregation of human platelets by a pathway insensitive to the presence of aspirin\(^{63}\). Using this system, the S(−)-trimetoquinol, which has little effect on the prostaglandin mediated platelet aggregation pathway, could also inhibit thrombin or phospholipase C (from Clostridium perfringens) mediated platelet aggregation. Whereas the R(+)–trimetoquinol was 3–3.5 fold less active in this system\(^{63}\).

These findings indicated that different stereoisomers of trimetoquinol selectively inhibit platelet aggregation via different mechanisms and through prostaglandin-dependent and independent pathways.
Figure 1. Proposed platelet aggregation pathways.

Modified from Navran (1981)
CHEMISTRY

Benzyllisoquinolines

Trimetoquinol is a tetrahydrobenzylisoquinoline derivative. The benzylisoquinolines make up an important segment of alkaloid chemistry. Naturally occurring benzylisoquinolines belong to two major groups. They are 1,2,3,4-tetrahydro benzylisoquinolines, such as reticuline (17) and the completely aromatic benzylisoquinolines, such as papaverine (18). Benzylisoquinolines also serve as biogenetic precursors to many other naturally occurring alkaloids including: isoquinolones, pavines, isopavines, bisbenzylisoquinolines, cularines, dibenzopyrrolcolines, morphines, cularine-morphine dimers, proporphines, aporphines, protoberberines, erythrina bases, and others.$$^{64-66}$$

![Chemical structures](image)

Benzylisoquinolines possess a variety of biological activities. For example, papaverine (18), a completely aromatic benzylisoquinoline, is a smooth muscle relaxant.$$^{67}$$ It
has been used to treat vasospasms accompanying peripheral aterial embolism, pulmonary embolism, and cerebrovascular thrombosis. Higenamine (19), was found to possess beta-adrenergic stimulating activity.

![Chemical Structures]

In 1966, Yamato et al. found that 1-(3',4'-dihydroxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydro-isoquinoline, (20) (N-norlaudanosoline, tetrahydropapaveroline), possessed a significant bronchodilating activity. This compound had been synthesized early in 1909 by Pyman, and its hypotensive activity was reported in 1910. It has also been demonstrated to be a biogenetic condensation product of dopamine (21) and its metabolite 3,4-dihydroxyphenylacetaldehyde (22) by Holtz (Scheme 2).
SCHEME 2

\[
\begin{align*}
21 \xrightarrow{\text{MONOAMINE OXIDASE}} & \quad 22 \\
\downarrow & \\
20 & \quad \text{SEVERAL STEPS} \\
& \quad 23
\end{align*}
\]

CH\textsubscript{3}CH\textsubscript{2}OH

CH\textsubscript{3}CHO

ALDEHYDE DEHYDROGENASE
Norlaudanosoline (20) is the requisite intermediate in the biosynthesis of morphine (23) in the opium poppy (Papaver somniferum). Since acetaldehyde, a metabolite of ethanol, which inhibits the enzyme aldehyde dehydrogenase, will prevent the normal metabolism to 6,7-dihydroxyphenylacetic acid (24) and thus will promote the production of N-norlaudanosoline. The N-norlaudanosoline has been proposed to be further converted to morphine-like alkaloids and this provides a basis for alcohol addiction\textsuperscript{74}.

This hypothesis has been seriously criticized by Seevers\textsuperscript{75}. The arguments are (a) no cross-tolerance between alcohol addiction and morphine addiction, (b) morphine users prefer barbiturates, amphetamines or cocaine over alcohol. However, recent studies did find cross-tolerance between ethanol and morphine in the Guinea pig ileum longitudinal muscle/myenteric plexus preparation\textsuperscript{76} and in the hypothermic effect study in rats\textsuperscript{77}. In addition, acetaldehyde itself does form tetrahydroisoquinoline addition products with epi-nepherine (3), norepinephrine (1), and dopamine (21) via a Pictet-Spengler type condensation through an unstable Schiff's base (Scheme 3):
The tetrahydroisoquinolines formed, such as salsolinol (25), as a resultant of alcohol ingestion may produce the hyperexcitability, tremulousness, hallucinosis and seizure of alcoholic patient\textsuperscript{78,79}. Low concentration of the crude condensates of acetaldehyde with epinephrine or norepinephrine also cause profound physiological and behavioral changes including complete depletion of guinea pig hypothalamic norepinephrine\textsuperscript{80} and selective degeneration of adrenergic nerves\textsuperscript{81} in laboratory animals. This activity of the mixture suggests that its constituents may indeed be responsible for some of the physiological effects of ethanol.
In order to investigate the relationship of structure to bronchodilating activity of N-norlaudanosoline, Iwasawa and Kiyomoto\textsuperscript{33} screened some sixty of 1-arylalkyl tetrahydroisoquinolines. Among them, 1-\((3,4,5\text{-trimethoxybenzyl})-6,7\text{-di-}
\text{hydroxy-1,2,3,4-tetrahydroisoquinoline (12, trimetoquinol, Inolin)}\) was observed to be the most active bronchodilator at that time, and it has been used clinically to treat asthma in Japan\textsuperscript{82}.

**Phenethylisoquinoline**

An example of phenethylisoquinoline, alkaloid that occurs in nature is autuminaline\textsuperscript{83} (26). It is the precursor of colchicine\textsuperscript{84} (27). The synthetic phenethylisoquinoline, methopholine\textsuperscript{85,86} (28), prepared in Hoffmann-La Roche laboratories\textsuperscript{86} is a safe analgesic. It gives analgetic effect equal to codeine, but does not cause addiction or constipation.
2- and 3- Tetrahydrobenzazepines

2-Tetrahydrobenzazepine alkaloids, such as schelhamerine (29), schelhamericine (30), Schelhammeridine (31) isolated from genus Cephalotaxus, belong to the homoery thrina family.

Some of the 3-tetrahydrobenzazepine alkaloids such as cephalotaxine (32), and other cephalotaxine alkaloids, are found in genus Cephalotaxus. Naturally occurring esters of cephalotaxine such as harrintonine (33) isoharringtonine (34), homoharringtonine (35), and deoxyharringtonine (36) all showed significant activity against leukemia in mice.
Synthetic 2- and 3-tetrahydrobenzazepines also possess a variety of pharmacological activities. For example, LY 134046 (37), is a potent inhibitor of N-methyltransferase (NMT) from rat brain or rabbit adrenal glands in vitro. Structurally, LY 134064 is similar to SKF 64139 (38), and they both are inhibitors of NMT in vitro and in vivo, but the two compounds differ in the relative abilities to block alpha-2 receptors. SKF 64139 is 20 to 50 fold more potent than LY 134064 in antagonizing alpha-2 receptors, yet it is only about twice as potent as LY 134064 in inhibiting NMT activity. In other words, LY 134064 is more selective than other currently known inhibitors of NMT and is a useful pharmacological tool in studying the intervention and function of epinephrine neurons in the brain.
SKF 38393(39), a 3-tetrahydrobenzazepine, is a dopamine receptor agonist. It selectively increases renal blood flow when administered i.v. to dogs at cumulative doses of 3.3 - 1333 μg/kg. Consistent changes in arterial blood pressure, heart rate and cardiac output were not observed. The renal response to 39, which is mediated locally in the kidney, was not antagonized by adequate blocking doses of the cholinergic antagonist atropine (40), beta antagonist propranolol (9), H-2 antagonist metiamide (41) or H-1 antagonist mepyramine (42). It indicates that SKF 38393, like dopamine, does not exert an effect on cholinergic receptors, beta-receptors or histamine (H-2 and H-1) receptors, respectively.
However, it was inhibited by the selective peripheral dopamine receptor antagonist, bulbocapnine (43)\(^{94}\). It stimulates the dopamine-sensitive adenyl cyclase in homogenates of rat caudate, as a partial agonist, and caused central-lateral rotation in rats with unilateral 6-hydroxydopamine (44) lesions of substantia nigra. In contrast to other dopamine agonists SKF 38393 did not cause stereotypy, emesis or inhibition of prolactin release, nor did it effect dopamine turnover. Therefore, it was suggested that SKF 38393 may selectively stimulate supersensitive central dopamine receptors in vivo or may activate only adenyl cyclase coupled postsynaptic dopamine receptors.
Another very interesting 3-tetrahydrobenazepine derivative (45), which was synthesized from the ring enlargement of the corresponding dihydroisoquinoline with zinc dust, possessed nonselective beta-1 and beta-2 adrenergic activities.95

Structure Activity Relationships of Trimetoquinol

The structure-activity relationship of trimetoquinol toward beta-adrenergic receptors has been studied for many years. Early in 1967, Iwasawa and Kiyomoto33 pointed out that the catechol group, the nitrogen atom and the aromatic ring of the arylmethyl group at position 1 of tetrahydroisoquinoline derivatives were essential for the beta adrenergic activity. Subsequently, Miller and Feller96,97,98 as well as Iwasawa and Kiyomoto99 reported that fragmented derivatives (46-49) of trimetoquinol, or hexahydrobenzo-\{d,e\}-quinoline derivatives of trimetoquinol100 (50) possess weak beta-adrenergic activity. Substitution at the 1-position of the tetrahydroisoquinoline ring moiety(51) provides beta adrenergic antagonists rather than agonists 101. Mono-hydroxy substitution at 3,4,5-trimethoxybenzyl position(52),(53) reduces potency102 and the three isomer (53) is even less active than the erythro isomer (52) on both beta-1 and beta-2 receptors. Mono-methyl substitution at the 3,4,5-trimethoxybenzyl position gave erythro methyl isomer (54) and three methyl isomer (55) of trimetoquinol
and the threo isomer (55) is more active and selective on beta-2 adrenergic receptors than trimetoquinol while the erythro isomer (54) is less active than trimetoquinol on both beta-1 and beta-2 adrenergic receptors.\textsuperscript{103}
The 3,4,5-trimethoxybenzyl moiety of trimetoquinol appears to be very important for beta adrenergic activity, since slight changes such as replacement with a 2,3,4-trimethoxybenzyl group (56) reduces potency.

Recently, Iwakuwa et al. reported that 5,7-dihydroxy (57) rather than 6,7-dihydroxy substitution of trimetoquinol provides a compound with twice the bronchial dilating activity, and also improves the bioavailability when administered intraduodenally. A ring enlarged trime-
toquinol analog (45) retains both beta-1 and beta-2 adrenergic activities. More interestingly, compound 45 also becomes a beta adrenergic antagonist.
Chapter II

STATEMENT OF PROBLEM AND OBJECTIVES

Tetrahydroisoquinolines represent a class of cyclized phenethylamines whose pharmacological properties are being more fully realized. Trimetoquinol (12) is a substituted tetrahydroisoquinoline whose pharmacological properties are well documented. The substance is used in Japan for relief of asthmatic bronchospasms\(^2\,^3\). The bronchodilating properties are associated with the stimulation of beta-adrenoceptors in the tracheal muscle. However, trimetoquinol has been shown to be a potent nonselective beta-agonist and thus also produces cardiac stimulation. Since Lands et al. has divided beta receptors into beta-1 (heart muscle) and beta-2 (bronchodilation), the overall objective of this research is to investigate new chemical modifications of trimetoquinol to determine whether such changes in the structure of the molecule will produce selective beta-2 adrenoceptor agonists. Also, the analogs should provide a better understanding of what portions of trimetoquinol are required for potent beta-1 or beta-2 adrenoceptor activity. Recently, it has been shown that R(+) Trimetoquinol is also a potent inhibitor of platelet aggregation and it is thought to act by antagonizing the action of thromboxane A2, (\(\text{TxA}_2\)), (13). Both
the R(+) - and the S(-)-trimetoquinol have also been shown to be antiaggregatory agents by inhibiting the phospholipase C mediated aggregation pathway on platelets. The compounds to be prepared should provide new insights into the structural requirements for either TXA₂ antagonist properties or phospholipase C inhibitory activity and how major separations may exist between beta adrenergic agonist and antiaggregatory activities.

We have prepared the following alpha-substituted TMQ derivatives (58-60):
We have prepared the 1- naphthyl TMQ analogs(61, 62):

We have also prepared the side chain extended compound(63). In addition, the synthetic sequences to 2- and 3-tetrahydrobenzazepine analogs of TMQ were investigated. We have prepared the following tetrahydrobenzazepine derivatives(64, 65, 66):
Chapter III
RESULTS AND DISCUSSION

SYNTHETIC APPROACH
The Alpha-Benzyllic Substituted Trimetoquinol Analogs

The first set of analogs to be discussed are those in which we have placed substitutions on the alpha-benzyl carbon of trimetoquinol. These studies were performed to extend the previous work in which it was observed that a methyl group substituted at this position provided selective beta-2 adrenergic activity. No work had previously been reported on disubstitution at the alpha-benzyl position of trimetoquinol. The synthesis of the dimethyl trimetoquinol analog plus extending the monomethyl to isopropyl substitution will be discussed.

Initially, methyl-(3,4,5-trimethoxy)phenylacetate (67) was alkylated using the procedure of Shamma and Jones. Dimethylation can be achieved in 56% yield by two successive methylations with no contamination of monomethylated product or the starting material. According to the NMR integration of the aromatic region, however, monoisopropylation by the same method gave a 10:1 mixture of isopropyl derivative and starting material which could not be separated either by co-
lumn chromatography or fractional distillation. Fortunately, at room temperature, the starting material was hydrolyzed in methanolic potassium hydroxide solution while the isopropyl derivative remained intact. This phenomenon can be explained by the Newman rule of six, which states that those atoms which are most effective in providing steric hindrance to addition are separated from the attacking atom in the transition state by a chain of four atoms. This means that if either the attacking atom or the carbonyl oxygen is designated as "1", the "blocking atom" will be in the "6" position. The isopropyl derivative, which has six blocking hydrogen atoms at the "6" position away from the carbonyl oxygen, was not hydrolyzed at room temperature while the starting material, which has no blocking atoms at the "6" position away from the carbonyl oxygen, was easily hydrolyzed at room temperature. By using this technique, pure isopropyl derivative 69 could be easily obtained in 61% yield. The hydrolysis of esters 68 and 69 was carried out in refluxing methanolic potassium or sodium hydroxide. Quantitative yields of the corresponding acids were obtained and then converted to the acid chlorides and then allowed to react with 3,4-dibenzylqoxphenethylamine(72) to give the corresponding amide 73 and 74. An attempt to prepare the amide 74 via direct heating of the acid 71 with amine 72 failed to give the desired amide. The alpha-dimethyltrimetoquinol analog (58) could be easily obtained by a Bischler-
Napieralski ring closure of the amide $73$ followed by sodium borohydride reduction and catalytic reduction (Scheme 4). However, Bischler-Napieralski ring closure and sodium borohydride reduction gave a 18:1 mixture of the erythro ($77$) and threeo ($78$) isopropyl isomers, which could be separated by column chromatography on silica gel. The major product, the erythro isomer, was converted to the desired isopropyl trimetoquinol analog ($59$) by catalytic reduction. The threeo isomer was prepared by a slight modification, that is the benzyl bromide salt of the imine $76$ was formed after ring closure and before sodium borohydride reduction. Although the total yield was only 50%, this modification resulted in a yield of erythro ($79$) to threeo ($80$) isomers in a ratio of 2:1 instead of 18:1 as was originally found from the sodium borohydride reduction. Catalytic hydrogenation of $80$ afforded the threeo isopropyl trimetoquinol analog ($60$) (Scheme 5).
SCHEME 4

67

1) NaNH₂/NH₃
2) CH₃I
or
(CH₃)₂CHBr

R₁ R₂

68 CH₃ CH₃
69 H (CH₃)₂CH

NaOH

70 CH₃ CH₃
71 H (CH₃)₂CH

1) SOCl₂
2)

BzI0

72

73 CH₃ CH₃
74 H (CH₃)₂CH
SCHEME 4 (Continued)

\[ \text{Reactions:} \]
1) \( \text{POCl}_3 \)  
2) \( \text{NaBH}_4 \)  
3) \( \text{HCl} \)

\[ \text{Chemical Structures:} \]
1. \( \text{73} \) 
2. \( \text{75} \) 
3. \( \text{58} \)
SCHEME 5 (Continued)

Bz1O
Bz1O

\[
\text{OCH}_3
\]
\[
\text{CH}_3
\]
\[
\text{CH}_3
\]

74

POCl

80

1) Bz1Br

2) NaBH

1) HCl

2) H₂/Pd/C

Bz1O
Bz1O

\[
\text{OCH}_3
\]
\[
\text{CH}_3
\]
\[
\text{CH}_3
\]

76

1) HCl

2) H₂/Pd/C

Bz1O
Bz1O

\[
\text{OCH}_3
\]
\[
\text{CH}_3
\]
\[
\text{CH}_3
\]

79

Bz1O
Bz1O

\[
\text{OCH}_3
\]
\[
\text{CH}_3
\]
\[
\text{CH}_3
\]

59

HO

HO

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

60

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

\[
\text{CH}_3
\]

\[
\text{CH}_3
\]

\[
\text{CH}_3
\]

\[
\text{CH}_3
\]
Owing to the successful assignments of the relative configurations of the C-13 and C-14 protons of C-13 substituted tetrahydro protoberberines 103,108,109, the two isomers 117 and 118 were treated with formaldehyde under Mannich conditions to afford the tetrahydro protoberberines 117 and 118 (scheme 6). The 300MHz NMR spectra showed a doublet for the C-14 proton at 3.66ppm for 117 and 3.67ppm for 118 respectively. The coupling constants between C-13 and C-14 protons are 5.5Hz for 117 and 2.6Hz for 118. Using Dreiding models the approximate dihedral angles between C-13 and C-14 protons as shown in scheme 6 are estimated as are ~180° for 117 and ~60° for 118, respectively. The coupling constant (J_{13,14}=2.6Hz) for 118 agrees with the proposed dihedral angle according to the Karplus relationship 111, whereas the coupling constant (J_{13,14}=5.5Hz) for 117 appears to be smaller than one would predict. However, the relative sizes of coupling constants are in agreement with the proposed assignment.

These data indicated that the C-13 and C-14 protons in 117 are in a trans relative configuration whereas in 118 they are in a cis relative configuration. The infrared spectrum of 117 did not show a Bohlmann band in the region of 3.5-3.7μ whereas 118 did show a Bohlmann band at 3.7μ indicating that the quinolizidine ring juncture of 117 is in a cis configuration whereas that of 118 is in a trans configuration 103,111,112.
From the data shown above, we proposed that compound 77 is indeed the erythro diastereoisomer whereas compound 78 is the three diastereoisomer\textsuperscript{108,109}.

**Scheme 6**

\[
\text{BzIO} \quad \text{HCHO} \quad \text{OCH}_3 \quad \text{OCH}_3
\]

77 → 81

\[
\text{BzIO} \quad \text{HCHO} \quad \text{OCH}_3 \quad \text{OCH}_3
\]

78 → 82
The 1-Naphthyl Substituted Trimetoquinol Analogs

The 1-naphthyl substituted trimetoquinol analogs 61 and 62 were prepared by using the same method as described for trimetoquinol. 1-Naphthoic acid(83) or 5,6,7-trimethoxy-2-naphthoic acid(84), were converted to their respective acid chlorides, and allowed to react with 3,4-dibenzylxoy phenethylamine(72) to give the corresponding amides 85 and 86. Cyclization by Bischler-Napieraski reaction followed by sodium borohydride and catalytic reduction afforded 61 and 62 (Scheme 7).
SCHEME 7

\[ \text{ArCOOH} \xrightarrow{1)} \text{SOCl}_2 \xrightarrow{2)} 72 \rightarrow \text{BzI0} \xrightarrow{1)} \text{POCl}_3 \xrightarrow{2)} \text{NaBH}_4 \]

83, 84

85, 86

\[ \text{BzI0} \xrightarrow{1)} \text{HCl} \xrightarrow{2)} \text{H}_2/\text{Pd/C} \rightarrow \text{HO-} \xrightarrow{1)} \text{NH}_2\text{Cl}^- \]

87, 88

61, 62

For 83, 85, 87, 61:

\[ \text{Ar} = \]

For 84, 86, 88, 62:

\[ \text{Ar} = \]

\[ \text{CH}_3\xrightarrow{-} \text{OCH}_3 \text{OCH}_3\]
The 1-Phenethyl Analog of Trimetoquinol

The phenethyl trimetoquinol analog (63) was synthesized in an analogous fashion by catalytic hydrogenolysis of the benzyloxy protecting group of the tetrahydroisoquinoline 91 which was synthesized via Bischer-Napieralski ring closure of the corresponding amide 90 followed by sodium borohydride reduction (Scheme 8).
SCHEME 8

72 + O-OH → TOLUENE

89

1) POCl₃
2) NaBH₄

90

91

1) HCl
2) H₂/Pd/C

63
The 2-Tetrahydrobenzazepine Analog of Trimetoquinol

The 2-tetrahydrobenzazepine analog of trimetoquinol (64) was the ring enlarged analog which had never been reported in the literature. It was prepared in a similar fashion as trimetoquinol. We have used both the methylenedioxy and dibenzyloxy as the protecting groups for the catechol moiety. These protecting groups are reported to be easily removed by boron trichloride\(^{113}\) and hydrogenolysis\(^{102}\), respectively.

The methylenedioxy series utilized methylenedioxyccinnamic acid (92) as starting material. The conjugated acid 92 was reduced with sodium amalgam to methylenedioxy phenylpropionic acid(93). The acid 93 was converted to the amide 94\(^{114}\) according to the method of McCarty et al.\(^{115}\) and then reduced with diborane to the corresponding amine 95\(^{116}\) which was then reacted with 3,4,5-trimethoxy phenylacetyl chloride to give amide 96. Bischler-Napieralski ring closure of amide 96 was accomplished in acetonitrile with three equivalent of phosphoryl chloride. Other solvents, such as benzene or toluene, with different reagents such as phosphorous pentoxide\(^{117}\) or aluminum chloride\(^{118}\) yielded either the starting materials or a yellowish gum. After diborane reduction of the imine formed, the 2-tetrahydrobenzazepine 97 failed to crystallize from the reaction mixture unless it was purified by column chromatograph on silica gel. The yield of 97 was only 15%. Boron trichloride cleavage of
the methylenedioxy group of 97 gave a relatively low yield and of the impure catechol 64 (Scheme 9).
SCHEME 9 (Continued)

\[ \text{97} \xrightarrow{\text{BCl}_3} \text{64} \]
The synthesis of the dibenzyloxy series was carried out by converting 3,4-dihydroxy dihydrocinnamic acid (98) to acid 99 which was converted to the amide 100 and reduced with diborane to the corresponding amine 101.\textsuperscript{119} The amide 101 was further converted to the N-(3,4-dibenzyloxyphenyl propyl)- 3,4,5-trimethoxy phenylacetamide (103). The Bischler-Napieralski ring closure of amide 103 followed by diborane reduction and column chromatography on silica gel afforded higher (35%) yield of amine 104. Hydrogenation of amine 104 gave pure crystalline catechol 64 (Scheme 10).
SCHEME 10 (Continued)

\[
\begin{align*}
\text{104} & \xrightarrow{\text{H}_2/\text{Pd/C}} \text{64}
\end{align*}
\]
The 3-Tetrahydrobenzazepine Analogs of Trimetoquinol

The 3-tetrahydrobenzazepine analogs of trimetoquinol (65) and (66) cannot be prepared via Bischler-Napieralski reaction directly. In order to construct the 3-benzazepine framework, we employed the intermolecular diazomethane iminium insertion followed by ring expansion originally reported by Leonard et al. Examples for this type of reaction were also reported by Goeber et al. for hydrastinine (105) and cotarine (106) to give the ring-expanded benzazepine derivatives 107 and 108 respectively (Scheme 11).

![Scheme 11](image)
However, when the benzyl bromide salt of imine 109 was treated with diazomethane, only the starting materials were recovered (Scheme 12).

**SCHEME 12**

\[ \text{BzI} \text{O} \text{N} \text{BzI} \text{Br} \rightarrow \text{CH}_{3} \text{N}_{2} \rightarrow \text{N}, \text{R.} \]

**SCHEME 13**

\[ \text{CH}_3 \text{O} \text{N} \text{CH}_3 \text{Br} \rightarrow \text{CH}_2 \text{N}_2 \rightarrow \text{CH}_3 \text{O} \text{N} \text{CH}_3 \text{O} \]

In 1974, Kametani et al.\textsuperscript{122} reported a diazomethane ring expansion of the iminoketone 110 to the dihydrobenzazepine 111 (Scheme 13). By using the benzyl bromide salt of iminoketone 112\textsuperscript{95}, which was the oxidation product of the corresponding imine, as starting material, ring expansion with diazomethane afforded two products 113 and 114 in contrast to one product in Kametani's work\textsuperscript{122}. The ratio of these two products varied with solvent, that is in tetrahydrofuran, 114 : 113 = 2:1; in methanol, 114 : 113 = 1:2; in dichloromethane, 114 : 113 = 1:1 (Scheme 14)
A possible mechanism for this result is proposed in which either the iminoketone 112 or its resonance form 115 was attacked by diazomethane and lead to the aziridium intermediate 116 and/or the cyclopropyl intermediate 117 which would further convert to 1-benzyl product 113 and 2-benzoyl product 114, respectively (Scheme 15).
SCHEME 15

Scheme showing chemical reactions involving aromatic and heterocyclic structures with various functional groups such as Br, N, and O. The reactions proceed with the addition of CH₂N₂, leading to the formation of compounds labeled as 112, 115, 116, 117, 113, and 114.

Each compound contains benzyl (Bzl) groups and various ester and ether functionalities.

- **112** (left) and **115** (right) are connected by an arrow, indicating a reaction pathway.
- **116** and **117** show the addition of CH₂N₂, with an intermediate structure before and after the reaction.
- **113** and **114** depict the final products after the reactions with CH₂N₂.

The molecular structures are detailed with precise attachment points and functional group notations.
A number of reducing agents have been used in attempts to reduce the conjugated carbonyl system in 113 and 114. Sodium borohydride in ethanol or triethylsilane in trifluoro acetic acid 126, 127 failed to produce any reduced product. Sodium borohydride in pyridine 128 gave 10% of the saturated alcohol 119 and 122 respectively. Mild reduction by using diborane in trifluoroacetic acid 129 for 10 minutes gave the saturated ketone 118 and 121 in >90% of yield from the respective iminoketone 113 and 114. Reduction of the ketone 118 and 121 with the Wolff-Kishner reaction by using hydrazine and potassium hydroxide in ethylene glycol 130 or potassium t-butoxide in dimethyl sulfoxide 131 or potassium carbonate in ethylene glycol 132 gave a mixture of unidentified decomposed products. Reduction of ketone 118 with tosylhydrazine and catecholborane 133 or with diborane and boron trifluoride-etherate 134 gave only the saturated alcohol 119 in low yield (30%). However, sodium borohydride in ethanol gave quantitative yield of alcohol 119 and 122 respectively. Attempts at further reduction of the alcohol 119 with a variety of methods including with (a) triethylsilane and boron trifluoride 135 (b) tosyl chloride followed by lithium aluminum hydride 136 or (c) thionyl chloride followed by lithium aluminum hydride 137 did not produce significant amount of the desired product. Only starting material could be obtained by treating alcohol 119 with potassium bisulfate, but when 119 was allowed to
react with p-toluenesulfonic acid, the stilbene 120 was isolated and hydrogenation afforded the catechol 65. Attempted dehydration of alcohol 122 using the same method failed. However, when the alcohol 122 was allowed to reacted with thionyl chloride followed by lithium aluminum hydride reduction 137 gave a 50% yield of the saturated compound 123. Finally, catalytic hydrogenation afforded the catechol 66 (Scheme 16 and Scheme 17).
SCHEME 16

$$\text{BzI} \rightarrow \text{N BzI}$$

$$\text{O} \rightarrow \text{O}$$

113 \[ \text{CH}_3 \text{O} \text{OCH}_3 \] 118 \[ \text{CH}_3 \text{O} \text{OCH}_3 \]

$$\text{BzI} \rightarrow \text{N BzI}$$

$$\text{N} \rightarrow \text{H}$$

119 \[ \text{CH}_3 \text{O} \text{OCH}_3 \]

$$\text{NaBH}_4$$

$$\text{PTSA}$$

$$\text{HO} \rightarrow \text{H}$$

119 \[ \text{CH}_3 \text{O} \text{OCH}_3 \]

$$\text{HO} \rightarrow \text{H}$$

120 \[ \text{CH}_3 \text{O} \text{OCH}_3 \]

$$\text{H}_2 / \text{Pd} / \text{C}$$

65 \[ \text{CH}_3 \text{O} \text{OCH}_3 \]

1) HCl

2) H$_2$/Pd/C
SCHEME 17

\[ \text{BzI0} \text{N} \text{BzI} \text{COO} \text{CH}_3 \text{OCH}_3 \xrightarrow{\text{B}_2\text{H}_6} \text{BzI0} \text{N} \text{BzI} \text{COO} \text{CH}_3 \text{OCH}_3 \]

\[ \text{NaBH}_4 \xrightarrow{} \]

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

\[ \text{BzI0} \text{N} \text{BzI} \text{OH} \xrightarrow{\text{SOCl}_2} \text{BzI0} \text{N} \text{BzI} \text{Cl} \]
\[ \xrightarrow{2) \text{LiAlH}_4} \]

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

\[ \text{BzI0} \text{N} \text{BzI} \text{HO} \text{O} \text{N} \text{H}_2\text{Cl}^- \]
\[ \xrightarrow{1) \text{HCl}} \]
\[ \xrightarrow{2) \text{H}_2/\text{Pd}/\text{C}} \]

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

\[ \text{CH}_3 \text{O} \text{OCH}_3 \]
The structures of the positional isomer 65 and 66 were determined by two methods:

(a) According to Kametani et al., 122, 123 when the 1-benzoyl-dihydro-3-benzazepine 111 was heated with phosphoryl chloride in dry toluene it afforded 12-chloro-5,6,7,7a-tetrahydro-2,3,9,10-tetramethoxy-7-methylindeno-(2,1-a)-3-benzazepine (124) (Scheme 18). Indeed, the 1-benzoyl dihydro 3-benzazepine 113 formed a cyclized product 125 when it was allowed to react with phosphoryl chloride while the 2-benzoyl dihydro 3-benzazepine 114 failed to react with phosphoryl chloride. (Scheme 19).
(b) By using the same synthetic approach, the methylenedioxy series of compounds were prepared. Catalytic hydrogenation afforded the secondary amine 133 and 137 respectively. The latter could be cyclized by the Mannich reaction to give the protoberberine type product 138 while the former could not. Amines 133 and 137 were converted with boron trichloride 113 to the corresponding catechols 65 and 66 respectively. This step also confirmed the relationship between the methylenedioxy series and the dibenzyloxy series (Scheme 20, Scheme 21 and Scheme 22).
SCHEME 20

1) POCl₃  
2) air, Δ  
3) BzlBr

CH₂N₂
SCHEME 21

128

\[ \begin{array}{c}
\text{O} \\
\text{N} \text{BzI} \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \xrightarrow{\text{B}_2\text{H}_6} \xrightarrow{\text{CF}_3\text{COOH}} \begin{array}{c}
\text{O} \\
\text{N} \text{BzI} \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \]

130

\[ \begin{array}{c}
\text{O} \\
\text{N} \text{BzI} \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \xrightarrow{\text{NaBH}_4} \begin{array}{c}
\text{HO} \\
\text{H} \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \xrightarrow{\text{PTSA}} \begin{array}{c}
\text{O} \\
\text{N} \text{BzI} \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \]

131

\[ \begin{array}{c}
\text{O} \\
\text{N} \text{BzI} \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \]

132

\[ \begin{array}{c}
\text{O} \\
\text{N} \text{BzI} \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \xrightarrow{1) \text{HCl}} \xrightarrow{2) \text{H}_2/\text{Pd} \text{ / C}} \begin{array}{c}
\text{O} \\
\text{N} \text{H}_2 \text{Cl}^+ \\
\text{O} \\
\text{CH}_3 \text{O} \\
\text{OCH}_3 \\
\end{array} \]

133
SCHEME 21 (Continued)

\[ \text{BCl}_3 \]

133 \[ \text{CH}_3\text{O} \text{OCH}_3 \]

\[ \text{HCHO} \]

N. R.

65 \[ \text{CH}_3\text{O} \text{OCH}_3 \]
SCHEME 22

129

\[ \text{B}_2\text{H}_6 + \text{CF}_3\text{COOH} \rightarrow \text{134} \]

130

\[ \text{NaBH}_4 \rightarrow \text{135} \]

\[ \text{SOCl}_2 \rightarrow \text{LiAlH}_4 \]

136

\[ \text{1) HCl} \]

\[ \text{2) H}_2/\text{Pd}/\text{C} \rightarrow \text{137} \]
SCHEME 22 (Continued)

\[ \text{BCl}_3 \]

\[ 137 \quad \xrightarrow{\text{HCHO}} \quad 66 \]
BIOLOGICAL RESULTS AND DISCUSSION

Evaluation of Compounds in Beta Adrenergic Tissues

Owing to the fruitful results in which the three- and erythro-alpha methyl trimetoquinol were shown to be more selective and/or more potent than the parent compound toward beta-2 adrenergic receptors\textsuperscript{103}, we evaluated the alpha dimethyl trimetoquinol (58) for the beta adrenergic activities in both guinea pig tracheal (beta-2) and atrial (beta-1) systems. Surprisingly, the dimethyl trimetoquinol (58) possesses only weak agonist activity in guinea pig trachea and is about 6000 fold less active than trimetoquinol (figure 2). This analog is inactive in atrial preparations (figure 3) and was found not to block the chronotropic action of isoproterenol at 10^{-4}M. These data show that the dimethyl trimetoquinol (58) retains beta-2 adrenergic tissue activity. However, the affinity for the beta-2 receptor is greatly reduced by the dimethyl substitution at the alpha benzylic position of trimetoquinol.
Figure 2. Dose response curve for (+) trimetoquinol (12) and the dimethyl analog (58) on the relaxation of guinea pig tracheal smooth muscle. (n=4-8)
Figure 3. Dose response curve for (+) trimetoquinol (12) and the dimethyl analog (58) on the spontaneously beating guinea pig right atrium. (n=4-8)
One portion of our work was directed toward increasing the bulk on the alpha substitution from methyl to isopropyl giving rise to erythro-(59) and threo-(60) alpha-isopropyl trimetoquinol. Preliminary experiments indicated that compound 59 and 60 were inactive as beta stimulants in the concentration range \(10^{-9}\) to \(10^{-6}\) M. In contrast to the erythro-(54) and threo-(55) monomethyl trimetoquinol, both the isopropyl diastereomers 59 and 60 were found to possess only weak activities in trachea requiring concentrations greater than \(10^{-5}\) M to produce relaxation (Figure 4). By comparison to (-)-isoproterenol(6), both 59 and 60 are considerably less active as stimulants of chronotropic responses in guinea pig right atrium. Compound 59 showed significant chronotropic activity at concentrations greater than \(10^{-7}\) M, and reached an intrinsic activity of 0.4 at \(10^{-4}\) M (Figure 5). In other experiments these compounds 59 and 60 did not significantly shift the concentration-response curves of isoproterenol on the chronotropic response of guinea pig atria. Also these compounds did not have antagonistic activity against (-)-isoproterenol on guinea pig tracheal smooth muscle preparation in concentrations up to \(3 \times 10^{-5}\) M.
Figure 4. Dose response curve for the erythro- (59) and threeo- (60) monoisopropyl trimetoquinol analogs on the relaxation of guinea pig tracheal smooth muscle. (n=4-5)
Figure 5. Dose response curve for the erythro-(59) and threeo-(60) monoisopropyl trimetoquinol analogs on the spontaneously beating guinea pig right atrium. (n=3)
The next set of compounds to be examined were those in which the 1-benzyl substituent was replaced by a 1-naphthyl substituent giving rise to 61 and 62. Both of these substances were inactive as agonists on guinea pig trachea (Figure 6) and only 61 was marginally effective at a concentration range of $10^{-7}$ to $3 \times 10^{-5}$M on atria (Figure 7). However 61 was found to be an inhibitor of the isoproterenol induced chronotropic response on atria. At $3 \times 10^{-5}$M, 61 shifted the dose response curve of (-)-isoproterenol to the right and reduced the maximal chronotropic response (Figure 8). In other experiments, these compounds did not have antagonistic activity against (-)-isoproterenol on guinea pig tracheal smooth muscle preparations in concentrations up to $3 \times 10^{-5}$M.
Figure 6. Dose response curve for trimetoquinol analogs 61 and 62 on the relaxation of guinea pig tracheal smooth muscle. (n=4-6)
Figure 7. Dose response curve for trimetoquinol analogs 61 and 62 on the spontaneously beating guinea pig right atrium. (n=3)
Figure 8. Effect of trimetoquinol analog 61 on the dose response curve of (-)-isoproterenol-d-bitartrate on the spontaneously beating guinea pig right auricle. (n=6)
Extending the side chain of trimetoquinol from 1-benzyl to 1-phenethyl afforded 63. This compound has no affinity and intrinsic activity on beta-2 adrenergic system at concentrations up to $10^{-6}$ M. Ring expansion of trimetoquinol by a methylene unit afforded the isomeric 64, 65 and 66. Compound 65 is a partial agonist on beta-2 receptors with an intrinsic activity of 0.4 and ED$_{50}$ value of $10^{-7}$ M. Compound 64 and 66 were considerably less active and produced relaxation at concentrations at $3 \times 10^{-6}$ M (Figure 9). On beta-1 receptors, compound 64 was inactive whereas compound 65 was marginally effective at concentration range from $10^{-8}$ to $3 \times 10^{-4}$ M (Figure 10). However, compound 65 showed antagonistic activity on both beta-1 and beta-2 receptors. At concentrations lower than $3 \times 10^{-6}$ M, the pK$_B$ values for 65 on guinea pig atria and trachea were 6.76 and 7.10 respectively whereas higher concentrations of 65 were found to give considerably lower pK$_B$ values (Table 1).
Figure 9. Dose response curve for the tetrahydrobenzazepine analogs of trimetoquinol 64, 65 and 66 on the relaxation of guinea pig tracheal smooth muscle (n=4-10)
Figure 10. Dose response curve for trimetoquinol analogs 64 and 65 on the spontaneously beating guinea pig right atrium. (n=4-7)
Table 1

Effect of Compound 65 on the Dose Response Relationships of (-)-Isoproterenol on Isolated Tracheal Smooth Muscle and Right Auricular Preparations

<table>
<thead>
<tr>
<th>Concentration of 65 (M)</th>
<th>pD₂ for Isoproterenol</th>
<th>pD₂</th>
<th>pK_B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Absence</td>
<td>Presence</td>
<td></td>
</tr>
<tr>
<td>I. Guinea Pig</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trachea</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10⁻⁷</td>
<td>7.65</td>
<td>7.30</td>
<td>0.35</td>
</tr>
<tr>
<td>10⁻⁶</td>
<td>8.48</td>
<td>7.35</td>
<td>1.13</td>
</tr>
<tr>
<td>10⁻⁵</td>
<td>7.95</td>
<td>7.15</td>
<td>0.8</td>
</tr>
<tr>
<td>II. Guinea Pig</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atria</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3x10⁻⁶</td>
<td>8.25</td>
<td>7.0</td>
<td>1.25</td>
</tr>
<tr>
<td>3x10⁻⁵</td>
<td>7.30</td>
<td>7.0</td>
<td>0.3</td>
</tr>
</tbody>
</table>

* pD₂=-logED₅₀ for (-)-isoproterenol in the absence or presence of inhibitor, (65), n=3

** ΔpD₂=pD₂ of isoproterenol in the absence of 65-pD₂ of isoproterenol in the presence of 65

*** pK_B=-log

\[
\frac{[I]}{\text{dose ratio}}
\]

dose ratio=antilog ΔpD₂

[I] = Molar concentration of inhibitor, (65)
In conclusion, the intact 1-benzyl tetrahydroisoquinoline moiety is essential for potent beta-1 and beta-2 adrenergic activity. By altering the 1-benzyl substitution of trimetoquinol to naphthyl substituent or extending the side chain as with the phenethyl derivative 63, or expanding the heterocyclic ring to a 2- or 3-tetrahydrobenzazepine analog as with 64, 65, and 66, we noted a reduction of beta-2 adrenergic activity. We have noted somewhat surprisingly that the beta adrenergic activity of trimetoquinol is quite sensitive to structural modification. By appropriate substitution one can go from selective beta-2 agonist to beta adrenergic blocking agents. The alpha-benzyllic position is a highly sensitive area. A monomethyl substitution at the alpha-benzyllic position has provided an increase of potency and/or selectivity toward beta-2 adrenergic system. Increasing the bulk to dimethyl or to mono-isopropyl groups has greatly reduced the beta-adrenergic activity.
Evaluation of Compounds in Human Platelet Preparations
Prostaglandin Dependent Pathway

Using U-46619, (15S)-hydroxy-11α, 9α-(epoxymethano)-prosta-5Z,13E-dienoic acid, a stable PGH$_2$ analog, as a thromboxane A$_2$ mimetic$^{150}$, three compounds 58, 64 and 97 have been studied for their ability to inhibit the aggregation of the prostaglandin dependent pathway in human platelet rich plasma preparations. Only compound 58, (DMTMQ), was able to block the aggregatory and secretory responses to U-46619. Compound 64, (DHBA), and compound 97, (MDBA), failed to block platelet activation by U-46619 at concentrations up to 400 μM. (Table 2)

Table 2
The Inhibitory Activity of Trimetoquinol and Related Analogs ** Against Aggregation Induced by U-46619 (2 μM)

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$(μM)+SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(-)-TMQ</td>
<td>11±4.4</td>
</tr>
<tr>
<td>R(+)-TMQ</td>
<td>0.14±0.06</td>
</tr>
<tr>
<td>DMTMQ(58)</td>
<td>790±6</td>
</tr>
<tr>
<td>DHBA(64)</td>
<td>*</td>
</tr>
<tr>
<td>MDBA(97)</td>
<td>*</td>
</tr>
</tbody>
</table>

* No activity up to a concentration of 400μM.

** This concentration of U-46619 was the minimum required to produce maximal irreversible platelet aggregation.

Modified from Navran (1981)$^{152}$
Prostaglandin Independent Pathway

Work from our laboratory has shown that S(-)-trimetoquinol is about 3 to 3.5 fold more potent as an inhibitor of phospholipase C or thrombin induced platelet aggregation than R(+)-trimetoquinol. Our compounds were also tested for their ability to modify platelet activation by thrombin and phospholipase C. Initial experiments indicated that these compounds were ineffective inhibitors of thrombin induced platelet activation and only the tetrahydro 2-benzazepine analogs of trimetoquinol and were able to inhibit phospholipase C induced aggregation. Each of these two compounds were also found to be more potent than S(-)-trimetoquinol as inhibitor of the phospholipase C induced response (Table 3). Compound \( \text{97, (MDBA)} \), represents the most potent analog and is 16.7 times more active than S(-)-trimetoquinol against phospholipase C induced aggregation.
Table 3
The Inhibitory Activity of Trimetoquinol and Related Analogs
Against Aggregation Induced by Phospholipase C (0.05U/mL)**

<table>
<thead>
<tr>
<th>Compound</th>
<th>IC$_{50}$ (µM)+SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>S(-)-TMQ</td>
<td>50±2</td>
</tr>
<tr>
<td>R(+) - TMQ</td>
<td>175±5</td>
</tr>
<tr>
<td>DMTMQ(58)</td>
<td>*</td>
</tr>
<tr>
<td>DHBA(64)</td>
<td>30±6</td>
</tr>
<tr>
<td>MDBA(97)</td>
<td>3±2</td>
</tr>
</tbody>
</table>

* No activity up to a concentration of 400 µM

** In the presence of 1 mM of aspirin

Modified from Navran (1981) $^{152}$
Biochemical Consequences of Phospholipase C Induced Platelet Aggregation

Studies were conducted to examine the effect of compound 97, (MDBA), and trimetoquinol isomers on the breakdown of phosphatidylinositol in platelet membrane by phospholipase C. The concentration dependent action of these compounds as inhibitors of phospholipase C induced phosphotidalinositol breakdown showed that the rank order of inhibitory potency is MDBA > S(-)-TMQ > R(+) -TMQ. The concentration range of the compounds is similar to that observed for the inhibition of platelet aggregation\(^{152}\).

It has been suggested that phosphatidic acid might be a mediator of phospholipase C induced platelet activation\(^{59,137}\). However, neither the trimetoquinol isomers nor MDBA could inhibit the phosphatidic acid synthesis at concentration range which produced phosphatidylinositol breakdown and platelet antiaggregatory effect\(^{152}\). These findings suggested that the breakdown of phosphatidylinositol, perhaps due to diacylglycerol formation, rather than the phosphatidic acid, plays the most important role in the phospholipase C pathway of platelet aggregation\(^{152}\).
Further study showed that the trimetoquinol isomers blocked both phospholipase C and low dose thrombin induced platelet aggregation whereas the tetrahydro 2-benzazepines, namely DHBA (64) and MDBA (97), blocked only the phospholipase C induced platelet aggregation. The difference among the trimetoquinol isomers and DHBA and MDBA on thrombin- and phospholipase C-induced platelet aggregation (Table 4) suggested that these compounds produce their effect via different mechanisms.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>The Inhibitory Activity of Trimetoquinol and Related Analogs Against Aggregation Induced by Thrombin (0.03U/mL)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound</td>
<td>IC(_{50}) (\mu M) ± SEM</td>
</tr>
<tr>
<td>S(-)-TMQ</td>
<td>50±7</td>
</tr>
<tr>
<td>R(+)-TMQ</td>
<td>150±10</td>
</tr>
<tr>
<td>DMTMQ(58)</td>
<td>*</td>
</tr>
<tr>
<td>DHBA(64)</td>
<td>*</td>
</tr>
<tr>
<td>MDBA(97)</td>
<td>*</td>
</tr>
</tbody>
</table>

* No activity up to a concentration of 400 \mu M

** In the presence of 1mM of aspirin

Modified from Navran (1981)\(^{152}\)
Chapter IV
EXPERIMENTAL

SYNTHETIC METHODS

All melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected. Infrared data were collected on a Beckman 4230 spectrophotometer. The NMR spectra were recorded on a Varian A-60A or a Brucker Model HX-90E or WM-300 NMR spectrometer utilizing tetramethyilsilane as the internal standard. The mass spectra were determined on a Du-Pont Model 491 mass spectrometer. Chemical analyses were determined by Galbraith Laboratories, Inc., Knoxville, T.N.

Methyl-2-methyl-2-(3,4,5-trimethoxyphenyl) propionate(68)

A 250 ml three-neck round bottom flask was fitted with an ammonia gas inlet, a dry ice condenser, a dropping funnel, a magnetic stirrer, and a dry ice-acetone cooling bath. Liquid ammonia (200 ml) was condensed and a small piece of sodium was added, resulting in a persistent deep blue co-
lor. The color was discharged by adding 40 mg of Fe(NO$_3$)$_3$·9H$_2$O crystals according to Fieser et al. Then 2.42 g (105 mmole) of sodium was added. After the deep color disappeared, a black-gray suspension of sodium amide in ammonia was obtained. A solution of 12 g (0.05 mole) methyl-(3,4,5-trimethoxy) phenyl acetate$^{103}$ in 50 ml of dry ether was added dropwise and stirred for 30 minutes. Methyl iodide 22 g (0.155 mole) in a dry ether solution was added dropwise and stirred for 3 hours. Ammonium chloride crystals 5.6 g (0.105 mole) was added and the resulting mixture was stirred overnight. The mixture was filtered, the solid was washed with ether and the ether layers were combined. The solvent was evaporated in vacuo and the residue showed a mixture of mono- and dimethylated methyl-(3,4,5-trimethoxy) phenyl acetate. Therefore, without purification the mixture was methylated again by repeating the above procedure using 1.73 g (75 mmole) of sodium and large excess of methyl iodide (25 ml). The product thus obtained was washed with 2 ml of hexane and crystallized from ether. Recrystallization from the ether gave 7.54 g (65%) of ester.

mp 85 - 86$^0$;

ir (KBr) cm$^{-1}$: 1725 (C=O);

nmr (CDCl$_3$) (ppm):

1.55 (s, 6H, ArC(CH$_3$)$_2$),

3.63 (s, 3H, COOCH$_3$),

3.81 (s, 9H, 3 x ArOCH$_3$),
6.48 (s, 2H, 2 x ArH);

m/e (EI): 268

Analysis for C\textsubscript{14}H\textsubscript{20}O\textsubscript{5}:

Calculated: C, 62.67; H, 7.51;

Found: C, 62.85; H, 7.58.

2-Methyl-2-(3,4,5-trimethoxyphenyl) propionic acid (70)

![Structural formula of compound 70]

A solution of 6 g (22 mmole) of the ester \textit{68} and 1.25 g (22 mmole) of potassium hydroxide in 50% aqueous methanol was refluxed overnight. The solvent was evaporated in vacuo and the resulting basic layer was transferred to a separatory funnel, washed with ether, and then acidified with 10% HCl. The product was extracted with several portions of chloroform, dried (MgSO\textsubscript{4}), and evaporated in vacuo to give a pale yellow oil which solidified upon standing. It was re-crystallized from chloroform-hexane to give 4.1 g (72%) of acid \textit{70} as needles.

mp 74-74.5\degree;

ir (KBr) cm\textsuperscript{-1}: 1695 (C=O);

nmr (CDCl\textsubscript{3}) (ppm)

1.60 (s, 6H, ArC(CH\textsubscript{3})\textsubscript{2})
3.84 (s, 3H, ArOCH₃),
3.86 (s, 6H, 2x ArOCH₃),
6.62 (s, 2H, 2x ArH);
9.35 (br, 1H, COOH).

m/e (EI): 254

Analysis for C₁₃H₁₈O₅:

Calculated: C, 61.41; H, 7.14;
Found: C, 61.63; H, 7.31.

N-(3', 4'-dibenzoyloxy-phenethyl)-2-methyl-2-(3,4,5— trimethoxyphenyl) propionamide (73)

To a 10ml dry THF solution of 3.5 g (13.8 mmol) of the acid 70 was added 1.64 g (13.8 mmole) of thionyl chloride and a few drops of pyridine. The precipitate that formed was removed by filtration. The filtrate was evaporated in vacuo to yield the acid chloride as an oil. The acid chloride was used without further purification.

To a mechanically stirred solution of 5.09 g (13.8 mmole) of 3,4-dibenzoyloxyphenethylamine (72) in 100 ml of chloroform was added 2.56 g (24 mmole) of potassium carbonate in 100
ml of water. Then the acid chloride described above in 10 ml of chloroform was added dropwise to the two phase mixture and allowed to stir for 3 hours. The chloroform layer was then separated from the aqueous phase, washed with 10% HCl, saturated NaHCO₃ and water, and dried with sodium sulfate. The solvent was removed under reduced pressure affording a colorless oil, which was chromatographed on silica gel (30 g). Elution with ethyl acetate afforded the 7.1 g (90%) amide 73 as a clear oil.

ir (KBr) cm⁻¹: 1650 (C=O);

nmr (CDCl₃) (ppm):

1.50 (s, 6H, ArC(CH₃)₂),
2.60 (t, 2H, ArCH₂, J=6.5 Hz)
3.37 (q, 2H, CH₂NH, J=6.5 Hz),
3.80 (s, 6H, 2 x ArOCH₃),
3.84 (s, 3H, ArOCH₃),
5.10 (s, 2H, ArCH₂O)
5.12 (s, 2H, ArCH₂O),
5.20 (broad, CONH)
6.35-7.00 (m, 5H, 5xArH),
7.10-7.50 (m, 10H, 10xArH);

m/e (EI): 569

Analysis for C₃₅H₃₉NO₆:

Calculated: C, 73.79; H, 6.90; N, 2.46;

Found: C, 73.52; H, 7.06; N, 2.39.
1-(α,α-Dimethyl-3,4,5-trimethoxybenzyl)-6,7-dibenzylxoy-1,2,3,4-tetrahydroisoquinoline (75):

To a solution of 4.87 g (8.6 mmole) of amide 73 in 100 ml of dry acetonitrile was added 3.94 g (25.7 mmole) of phosphoryl chloride and the solution was allowed to reflux under Argon for 5 hours. After the solution was cooled, the solvent and excess of phosphoryl chloride was removed in vacuo. The resulting oil was taken up in chloroform and rapidly washed with 10% NaHCO₃ and water. After drying with sodium sulfate, the solvent was removed in vacuo to yield imine 76 as an oil (ir 1580 cm⁻¹), which was used without further purification. To a solution of the imine 76 in 50 ml of absolute methanol was added 3.24 g (0.083 mole) of sodium borohydride portionwise over 0.5 hour. The solution was then allowed to stir for one hour. The solvent was then removed in vacuo. The white residue was suspended in water and extracted with several portions of chloroform. The combined chloroform layers were washed with water and dried with magnesium sulfate. Removal of the solvent under reduced pressure yielded 4.55 g (96%) of 75. The white crystalline HCl salt was recrystallized from methanol.
mp 223-224°;

ir (neat, free base) cm$^{-1}$, 3360(NH), 1580(aromatic)

nmr (CDCl$_3$) (ppm):
1.23 (s, 3H, ArCH$_3$)
1.27 (s, 3H, ArCH$_3$)
2.06 (br, 1H, NH)
2.30-3.30 (m, 4H, ArCH$_2$CH$_2$)
3.78 (s, 6H, 2xArOCH$_3$),
3.82 (s, 3H, 1xArOCH$_3$),
4.33 (s, 1H, ArCHNH),
4.82 (s, 2H, ArCH$_2$O),
5.10 (s, 2H, ArCH$_2$O),
6.24 (s, 1H, 1xArH),
6.45 (s, 2H, 2xArH),
6.61 (s, 1H, 1xArH),
7.25-7.55 (m, 10H, 10xArH).

Analysis for C$_{39}$H$_{39}$N$_1$O$_5$·HCl:

Calculated: C, 71.23; H, 6.83; N, 2.37;

Found: C, 71.37; H, 7.00; N, 2.36.
1-(α,α-Dimethyl-3,4,5-trimethoxybenzyl)-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (58)

A mixture of 0.3 g (0.81 mmole) of 1-(α,α-Dimethyl-3,4,5-trimethoxybenzyl)-6,7-dibenzylxoy-1,2,3,4-tetrahydroisoquinoline (75) as the HCl salt and 110 mg of 10% Pd/C in 100 ml of absolute methanol was hydrogenated at 40 psi for 5 hour. The mixture was then filtered through celite and the filtrate was evaporated in vacuo. The resulting glassy residue was triturated in dry ether to yield a white solid, which was crystallized from methanol-ether to afford 140 mg (67%) of the white solid 58.

mp 253-255° (decomposed);
ir (HCl salt, KBr) cm⁻¹: 3380 (OH), 1590 (aromatic)
nmr (HCl salt, CD₃OD) (ppm):
  1.38 (s, 3H, ArC-C-CH₃),
  1.46 (s, 3H, ArC-C-CH₃)
  2.50-3.50 (m, ArCH₂CH₂, overlapped with solvent peaks)
  3.78 (s, 3H, ArOCH₃),
  3.81 (s, 6H, 2xArOCH₃),
  4.76 (s, 1H, ArCHNH),
6.51 (s, 1H, ArH),
6.58 (s, 2H, 2 x ArH),
6.61 (s, 1H, ArH);

Analysis for C_{21}H_{27}NO_{5}·HCl
Calculated: C, 61.53; H, 6.89; N, 3.42;
Found: C, 61.26; H, 7.00; N, 3.31.

Methyl 3-methyl-2-(3,4,5-trimethoxyphenyl) butanoate (69)

Using the procedure of Shamma and Jones\textsuperscript{108} 10 g (41.7 mmole) of ester 67 was alkylated with 5.66 g (46 mmole) of isopropyl bromide to give 5.91 g of a 10:1 mixture of the product and starting material. It was dissolved in 50% aqueous methanol and to this solution was added 95 mg of potassium hydroxide in 50% aqueous methanol and stirred at room temperature for 36 hours. After evaporation in vacuo, the residue was taken into ether and washed with water. The ether layer was evaporated in vacuo to afford 8.6 g (73%) of the pure ester 69.

bp 128-131°C/0.4 mmHg
ir (neat) cm\(^{-1}\): 1700 (C=O)
nmr (CDCl₃) (ppm):

0.73 (d, 3H, ArCHCHCH₃, J=6.7 Hz),
1.02 (d, 3H, ArCHCHCH₃, J=6.4 Hz),
2.05-2.45 (m, 1H, ArCHCH(CH₃)₂)
3.05 (d, 1H, ArCHCH(CH₃)₂, J=11.7 Hz),
3.67 (s, 3H, ArOCH₃),
3.83 (s, 3H, ArOCH₃),
3.85 (s, 6H, ArOCH₃),
6.55 (s, 2H, 2 x ArH);

Analysis for C₁₅H₂₀O₅:
Calculated: C, 63.81; H, 7.85;
Found: C, 63.94; H, 7.83.

3-Methyl-2-(3,4,5-trimethoxyphenyl) butanoic acid(71)

Methyl-3-methyl-2-(3,4,5-trimethoxyphenyl) butanoate (69)
8.6 g (30.5mmole) was mixed with 50% aqueous methanol and 1.63 g (29 mmole) KOH. After refluxing overnight, the mixture was evaporated in vacuo and the residue was washed with ether. The ether layer still contained 2.1 g of starting ester.
Therefore, it was saved and dissolved in 33% aqueous methanol and 300 mg of NaOH was added, the mixture was heated at reflux for 3 hours. After evaporation the mixture was washed with ether, no starting material was observed. The aqueous layers were combined and acidified with diluted HCl and extracted with chloroform. The chloroform layer was then dried with magnesium sulfate and evaporated in vacuo to give an oil which was crystallized from Chloroform-hexane to afford 6.6 g (80.3%) of the acid 71.

mp 98-100 °C;

ir (neat) cm⁻¹: 1700 (C=O)

nmr (CDCl₃) (ppm):

0.72 (d, 3H, ArCHCH₃, J=6.7 Hz),
1.06 (s, 3H, ArCHCH₃, J=6.4 Hz),
2.05-3.00 (m, 1H, ArCHCH(CH₃)₂)
3.04 (d, 1H, ArCHCH(CH₃)₂, J=10.8 Hz),
3.81 (s, 3H, ArOCH₃),
3.83 (s, 6H, 2xArOCH₃),
6.54 (s, 2H, 2 x ArH);
10.95 (br, H, COOH);

Analysis for C₁₄H₂₀O₅:

Calculated: C, 62.67; H, 7.51;

Found: C, 62.85; H, 7.47.
N-(3,4-Dibenzoyloxyphenethyl)-3-methyl-2-(3,4,5-trimethoxyphenyl) butyronamide (74)

A 50ml chloroform solution of 2.18 g (8.14 mmole) of the acid 71 and 1.93 g (16.3mmole) of thionyl chloride was refluxed overnight. The infrared spectrum showed a carbonyl absorption at 1790 cm⁻¹ (acid chloride). The solvent and excess of thionyl chloride were evaporated in vacuo. The residue was taken into chloroform and dropped simultaneously with 3,4-dibenzoyloxyphenethylamine in chloroform at refluxing temperature overnight. After being allowed to come to room temperature, the mixture was washed with diluted HCl, aqueous sodium bicarbonate solution and dried with magnesium sulfate. Solvent was then removed in vacuo and the residue was cleaned by column chromatography on silica gel using 10% ether in chloroform as eluent to yield 3.84 g (81%) of the amide 74 as an oil which solidified upon standing.

mp 98 - 99°C;

ir (neat) cm⁻¹: 3320 (NH), 1655 (C=O)

nmr (CDCl₃) (ppm):
0.70 (d, 3H, ArCHCH₃, J=6.4 Hz),
0.97 (d, 3H, ArCHCH₃, J=6.0 Hz),
2.14-2.74 (m, 4H, ArCHCH(CH₃)₂, and CH₂)
3.23-3.57 (m, 2H, CH₂)
3.82 (s, 9H, 3×ArOCH₃), 5.11 (s, 4H, 2×ArCH₂O) 5.48 (br, 1H, CONH) 6.36-6.88 (m, 5H, 5×ArH) 7.20-7.50 (m, 10H, 10×ArH)

Analysis for C₃₆H₄₁NO₆
Calculated: C, 74.08; H, 7.08; N, 2.40; Found: C, 73.98; H, 7.18; N, 2.40.

Erythro- and Threo- 1-(α-isopropyl-3,4,5-trimethoxybenzyl) 6,7-dibenzylxyloxy-1,2,3,4-tetrahydroisoquinoline (77), (78)

To a solution of 1.5 g (2.57 mmole) of the amide 74 in 100 ml of dry acetonitrile was added 1.19 (7.72 mmole) of POCl₃, and the solution was allowed to reflux under Argon for four hours. After the solution was cooled, the solvent and excess POCl₃ were removed under reduced pressure. Without further purification, the mixture was taken into absolute ethanol, cooled to 0°C, and 1 g (25.7 mmole) of sodium borohydride was added portionwise. The mixture was then al-
allowed to stir at room temperature overnight. The solvent was then removed *in vacuo* and the white residue was suspended in water and extracted with chloroform. The chloroform layer was washed with aqueous sodium bicarbonate, dried with magnesium sulfate and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel by using 7% methanol in chloroform (with 1% concentrated ammonium hydroxide) and upon elution the *erythro* isomer 775 mg (53.2%) and the *threo* isomer 44 mg (3%), respectively, were obtained. Total yield for two steps: 56%. From the free bases the HCl salts were prepared and were recrystallized from dichloromethane-hexane.

For the *erythro* isomer 77:

mp 153-154 °C;

ir (neat, free base) cm⁻¹: 3400 (br, NH), 1585 (aromatic)

nmr (free base, CDCl₃) (ppm):

0.84 (d, 3H, ArCHCHCH₃, J=6.3 Hz),
1.11 (d, 3H, ArCHCHCH₃, J=6.3 Hz),
1.58 (s, 1H, NH),
1.90-3.20 (m, 6H, 2xCH₂, 2xCH)  
3.63 (s, 6H, 2xArOCH₃),
3.78 (s, 3H, 1xArOCH₃),
4.38 (d, 1H, ArCHNH, J=3.5 Hz)
5.08 (s, 2H, 1xArCH₂O)
5.17 (d, 1H, 1/2xArCH₂O, J=11.7 Hz),
5.26 (d, 1H, 1/2xArCH₂O, J=11.7 Hz),
6.13 (s, 2H, 2 x ArH)
6.51 (s, 1H, 1 x ArH)
6.82 (s, 1H, 1 x ArH)
7.30-7.70 (m, 10H, 10 x ArH)

Analysis for C_{36}H_{41}NO_{5}.HCl:
Concrete: C, 71.57 ; H, 7.01 ; N, 2.32 ;
Found: C, 71.72 ; H, 7.17 ; N, 2.24 .

For the three isomer 78:
mp 113-115 °C;
ir (neat, free base) cm\(^{-1}\): 3300 (br,NH), 1585 (aromatic)
nmr (free base, CDCl\(_3\)) (ppm)
0.67 (d, 3H, ArCHCHCH\(_3\), J=6.4 Hz),
0.91 (d, 3H, ArCHCHCH\(_3\), J=6.4 Hz),
1.55-3.20 (m, 7H, 2xCH\(_2\), 2xCH and NH)
3.64 (s, 6H, 2xArOCH\(_3\)),
3.80 (s, 3H, 1xArOCH\(_3\)),
4.29 (d, 1H, ArCHNH, J=4.8 Hz)
5.06 (s, 2H, 1xArCH\(_2\)O)
5.11 (s, 2H, 1xArCH\(_2\)O)
6.01 (s, 2H, 2 x ArH)
6.58 (s, 2H, 2 x ArH)
7.20-7.55 (m, 10H, 10 x ArH)

Analysis for C_{36}H_{41}NO_{5}.HCl:
Concrete: C, 71.57 ; H, 7.01 ; N, 2.32 ;
Found: C, 71.29 ; H, 7.18 ; N, 2.28 .
Erythro-1-(α-isopropyl-3',4',5'−trimethoxybenzyl)−6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (59)

To a 50ml absolute ethanol solution of 350mg (0.58mmole) of 77 was added 80 mg of 10% Pd/C. The mixture was hydrogenated at 40 psi for 23 hr. and allowed to filter through celite. The filtrate was evaporated under reduced pressure and the residue was washed with ether. Upon crystallization of the residue from ethanol-ether 213 mg (76%) of the catechol HCl 59 was collected.

mp 215-218°C;

ir (HCl salt, KBr) cm⁻¹: 3400-3200 (br, NH and OH)
nmr (CD₃OD) (ppm):
0.92 (d, 3H, ArCHCHCH₃, J=6.7 Hz),
1.03 (d, 3H, ArCHCHCH₃, J=6.7 Hz),
1.90-2.40 (m, 1H, ArCHCH(CH₃)₂)
2.70-3.60 (m, 5H, 2xCH₂, 1xCH)
3.82 (s, 3H, 1xArOCH₃),
3.85 (s, 6H, 2xArOCH₃),
6.51 (s, 2H, 2xArH)
6.62 (s, 1H, 1x ArH)
6.82 (s, 1H, 1x ArH)
Analysis for $C_{22}H_{29}NO_5\cdot HCl$:

Calculated: C, 62.33; H, 7.13; N, 3.30;


*N-Benzylerthro-1-(α-isopropyl-3',4',5'-trimethoxybenzyl)*
-6,7-dibenzyloxy-1,2,3,4-tetrahydroisoquinoline (79)

A 25ml benzene solution of 60mg (0.1 mmole) of the erythro isomer of tetrahydroisoquinoline 77 and 25mg (0.2mmole) of benzyl bromide (0.2 mmole) were allowed to heat at reflux overnight. The solvent was then removed under reduced pressure, the residue was taken into chloroform and washed with aq. NaHCO$_3$ and dried (MgSO$_4$), and evaporated to give a residue that was purified by column chromatograph on silica gel using 5% ether/chloroform as eluent. The residue was crystallized from ethanol and afforded 42 mg (60%) of 79.

mp 129 -130°C;

ir (free base, neat) cm$^{-1}$: 1595 (aromatic)

nmr (free base, CDCl$_3$) (ppm):

0.78 (t, 6H, 2xArCHCH$CH_3$, J=6.0 Hz),
1.80-2.80 (m, 6H, ArCH₂CH₂N and ArCHCH(CH₃)₂)
3.66 (s, 6H, 2xArOCH₃),
3.83 (s, 3H, 1xArOCH₃),
3.94 (d, 1H, ArCHN),
5.13 (s, 2H, ArCH₂O),
5.16 (d, 1H, 1/2x ArCH₂O, J=16.2 Hz),
5.26 (d, 1H, 1/2x ArCH₂O, J=16.2 Hz),
6.08 (s, 2H, 2xArH)
6.61 (s, 1H, 1x ArH)
6.69 (s, 1H, 1x ArH)
7.05-7.56 (m, 10H, 10xArH)

Analysis for C₄₃H₄₇NO₅:
Calculated: C,78.50 ; H,7.20 ; N,2.13 ;
Found: C,78.77 ; H,7.40 ; N,2.09 .

N-Benzyl-threo-1-(α-isopropyl-3',4',5'-trimethoxybenzyl)
-6,7-dibenzylxoxy-1,2,3,4-tetrahydroisoquinoline (80)

A 100ml acetonitrile solution of 2.02 g (3.47 mmole) of
amide 74, and 1.76 g(11.4mmole) of phosphoryl chloride were
heated at reflux under Argon for 3.5 hours. After allowing to come to room temperature, the solvent was removed in vacuo. The residue was taken into chloroform, washed with aqueous sodium bicarbonate, dried with magnesium sulfate under an Argon atmosphere, and evaporated in vacuo. The residue was then dissolved in dry toluene and 4 g (34 mmole) of benzyl bromide was added. The mixture was refluxed under Argon for 48 hours and allowed to come to room temperature. The solvent was evaporated in vacuo and the residue was taken into absolute ethanol. Then sodium borohydride, 1.35 g (34.7 mmole), was added and the mixture was heated for 2 hours. The solvent was removed in vacuo. The yellowish residue was dissolved in chloroform, washed with aqueous sodium bicarbonate, dried with magnesium sulfate, and evaporated in vacuo. The residue was purified by column chromatography on silica gel using 5% ether in chloroform (with 1% ammonium hydroxide) as eluent. The free base of the threo isomer was obtained and converted to 364 mg (15%) of HCl salt of 80.

mp 95 -96 °C;

ir (free base, neat)cm⁻¹: 1590 (aromatic)

nmr (free base, CDCl₃) (ppm):

0.68 (d, 3H, 1×CHCH₂, J=6.7 Hz),
0.85 (d, 3H, 1×CHCH₂, J=6.7 Hz),
1.50-3.10 (m, 6H, ArCH₂CH₂N and ArCHCH(CH₃)₂)
3.62 (s, 6H, 2×ArOCH₃)
3.77 (s, 3H, 1×ArOCH₃)
3.50-4.0 (m, 3H, ArCHNCH₂Ar),
4.86 (s, 2H, ArCH₂O),
5.07 (s, 2H, ArCH₂O),
5.94 (s, 2H, 2xArH)
6.21 (s, 1H, 1x ArH)
6.55 (s, 1H, 1x ArH)
7.25-7.50 (m, 15H, 15xArH)

Analysis for C₄₃H₄₇N₀₅:
Calculated: C, 78.51; H, 7.20; N, 2.13;
Found: C, 78.32; H, 7.38; N, 2.05.

The erythro isomer 79 was also isolated in a later fraction from the column chromatography and afforded 770 mg (29%) of the free base 79.

Threo – 1-(α-isopropyl–3’,4’,5’-trimethoxybenzyl)-6,7—dihydroxy-1,2,3,4-tetrahydroisoquinoline (60)

![Chemical Structure](image)

To a 50ml absolute ethanol solution of 170 mg (0.25 mmole) of the HCl salt of N-benzyl threo precursor was added 85mg of 10% Pd/C and the mixture was hydrogenated at 40 psi
at room temperature overnight. The mixture was then filtered through celite, and the solvent was removed in vacuo. The residue was crystallized from ethanol-ether, and afforded 76 mg (73%) of the threo isomer 60 as HCl salt. mp 212-213°C;

ir (HCl salt, KBr) cm⁻¹: 3400-3200 (br, NH and OH)

nmr (HCl salt, CD₃OD) (ppm):
0.76 (d, 3H, 1xCHCH₃', J=6.4 Hz),
1.33 (d, 3H, 1xCHCH₃', J=6.4 Hz),
2.00-3.13 (m, 6H, ArCH₂CH₂N and ArCHCH(CH₃)₂)
3.62 (s, 6H, 2xArOCH₃),
3.72 (s, 3H, 1xArOCH₃),
4.92 (m, ArCHN, overlapped with the solvent peaks)
6.06 (s, 2H, 2xArH)
6.56 (s, 1H, 1x ArH)
6.81 (s, 1H, 1x ArH)

Analysis for C₂₂H₂⁹NO₅.HCl:

Calculated: C, 62.33; H, 7.13; N, 3.30;

Found: C, 62.13; H, 7.22; N, 3.31.
trans-13-Isopropyl-9,10,11-trimethoxy-tetrahydroprotoberine (81).

To a 50ml ethanol solution of 500mg (0.83mmole) of the HCl salt of the erythro isomer 77 was added 3.4ml (4.14mmole) of 37% formaldehyde solution and the mixture was heated at reflux overnight. After allowing the mixture to come to room temperature, the solvent was removed in vacuo and the residue was taken into chloroform and washed with water. The chloroform layer was dried (MgSO₄) and evaporated in vacuo. The residue thus formed was purified by column chromatography on silica gel using 10% ether in chloroform (with 1% ammonia water) as eluent to give the free base of 81. The HCl salt was prepared and recrystallized from ethanol to give 398mg (78%) of 81.

mp 129-131°C;
ir (free base, 5% W/V in chloroform) cm⁻¹: 1610, 1590 (aromatic).
nmr (free base, CDCl₃)(ppm):
0.70 (d, 3H, 1xCHCH₃, J=6.7 Hz),
1.09 (d, 3H, 1xCHCH₃, J=6.7 Hz),
1.60-2.25 (m, 1H, ArCHCH(CH₃)₂)
2.45-3.20 (m, 5H, ArCH$_2$CH$_2$N and ArCHCHN)
3.46 (d, 1H, 1/2xArCH$_2$N, J$_{gem}$=15Hz)
3.66 (d, 1H, ArCHN, J=5.5Hz)
3.81 (s, 3H, 1xArOCH$_3$),
3.82 (d, 1H, 1/2xArCH$_2$N, J$_{gem}$=15Hz)
3.83 (s, 6H, 2xArOCH$_3$),
5.12 (s, 4H, ArCH$_2$O)
6.38 (s, 1H, 1xArH)
6.64 (s, 1H, 1x ArH)
6.81 (s, 1H, 1x ArH)
7.20-7.60 (m, 10H, 10xArH)

Analysis for C$_{37}$H$_{41}$N$_1$O$_5$·HCl

Calculated: C,72.12 ; H,6.87 ; N,2.27 ;

Found: C,71.90 ; H,6.98 ; N,2.22 .

cis-13-Isopropyl-9,10,11-trimethoxy- tetrahydroprotoberine(82)

To a 5ml ethanol solution of 33mg(0.055mmole) of the HCl salt of the three isomer 78 was added 0.5ml (0.28mmole) of 37% formaldehyde solution and the mixture was heated at re-
flux overnight. After allowing to come to room temperature, the solvent was removed in vacuo and the residue was taken into chloroform and washed with water. The chloroform layer was dried (MgSO₄) and evaporated in vacuo. The residue thus formed was purified by column chromatography on silica gel using 10% ether in chloroform (with 1% ammonia water) as eluent to give the free base of 82. The HCl salt was prepared and recrystallized from ethanol to give 25mg (73%) of 82.

mp 177 -179° C;

ir (free base, 5% W/V in chloroform) cm⁻¹: 2750 (Bohllmann band)

nmr (free base, CDCl₃)(ppm):

0.57 (d, 3H, 1xCHCH₃, J=6.7 Hz),
0.78 (d, 3H, 1xCHCH₃, J=6.7 Hz),
1.25-1.85 (m, 1H, ArCHCH(CH₃)₂)
2.35-3.15 (m, 5H, ArCH₂CH₂N and ArCHCHN)
3.36 (d, 1H, 1/2xArCH₂N, J⁹⁰=15.6Hz)
3.67 (br, 1H, ArCHN, J=2.6Hz)
3.87 (s, 3H, 1xArOCH₃),
3.90 (s, 6H, 2xArOCH₃),
4.04 (d, 1H, 1/2xArCH₂N, J⁹⁰=15.6Hz)
5.14 (s, 4H, ArCH₂O)
6.43 (s, 1H, 1xArH)
6.71 (s, 1H, 1x ArH)
6.79 (s, 1H, 1x ArH)
7.15-7.55 (m, 10H, 10xArH)
Analysis for \( C_{37}H_{41}N_{10}O_5 \cdot HCl \)

Calculated: C, 72.12; H, 6.87; N, 2.27;
Found: C, 72.03; H, 6.92; N, 2.25.

\( \text{N-}(3,4\text{-dibenzoyloxyphenethyl})\text{-naphthylamide (85)} \)

A 100ml chloroform solution of 2.85g (15mmole) 1-naphthoic acid and 4g (33.6 mmole) of thionyl chloride was heated at reflux for 3 hr until the acid peak at 1675 cm\(^{-1}\) in IR spectrum disappeared. After the excess thionyl chloride and solvent were removed in vacuo the residue was dissolved in 10 ml of freshly distilled chloroform and dropped simultaneously with a chloroform solution of 5g (15mmole) of 3,4-dibenzoyloxyphenethylamine at 60\(^\circ\)C and refluxed overnight. The mixture was allowed to cool to room temperature, washed with aqueous NaHCO\(_3\) and dilute HCl and dried (MgSO\(_4\)). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel using 10% ether in chloroform as eluent and 4.13g (57%) of the pure amide 85 was isolated.

mp 126-127.5\(^\circ\)C

ir (neat)cm\(^{-1}\): 3290(NH), 1637(C=O).
nmr (CDCl₃) (ppm):
2.89 (t, 2H, ArCH₂, J=6.6Hz)
3.75 (m, 2H, CH₂NH)
5.08 (s, 2H, ArCH₂O)
5.13 (s, 2H, ArCH₂O)
5.89 (br, 1H, NH)
6.65-6.95 (m, 3H, 3xArH)
7.15-8.95 (m, 17H, 17xArH)

Analysis for C₃₃H₂₉NO₃
Calculated: C, 81.29; H, 6.00; N, 2.87;
Found: C, 81.25; H, 6.06; N, 2.72.

1-Naphthyl-6,7-dibenzylxyloxy-1,2,3,4-tetrahydroisoquinoline
(87)

A 200ml acetonitrile solution of 1.5g (3.08mmole) of the amide 85 and 1.42g (9.24mmole) of Phosphoryl chloride were heated at reflux under Argon atmosphere for 4 hr. The solvent and excess of phosphoryl chloride were evaporated in vacuo and the residue was dissolved in absolute ethanol, al-
lowed to cool to 0°C. To the ethanol solution was added 1.2g (30.8mmole) of sodium borohydride. After heating at reflux for 2 hr, the solvent was removed and the residue was taken into chloroform, washed with aqueous NaHCO₃ and dried (MgSO₄). The HCl salt was prepared and crystallized from ethanol-ether to afford 0.75g (52%) of 87.

mp 220-222°C

ir (free base, neat) cm⁻¹: 3320(NH), 1610(aromatic).

nmr (CDCl₃) (ppm):
1.83 (s, 1H, NH)
2.70-3.35 (m, 4H, CH₂CH₂)
4.82 (s, 2H, ArCH₂O)
5.14 (s, 2H, ArCH₂O)
5.78 (s, 1H, ArCHN)
6.36 (s, 1H, ArH)
6.76 (s, 1H, ArH)
7.00-8.30 (m, 17H, 17xArH)

Analysis for C₃₃H₂₉NO₂·HCl
Calculated: C, 78.02; H, 5.96; N, 2.76;
Found: C, 77.84; H, 6.08; N, 2.60.
1-Naphthyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline
(61)

\[
\text{HO} \quad \text{HO} \\
\text{NH} \\
\text{61}
\]

To a 50 ml absolute ethanol solution of 200mg (0.39mmole) of the HCl salt of amine 87 was added 100mg of 10% Pd/C and the mixture was hydrogenated at 40 psi overnight. The catalyst was removed by filtration through celite. The filtrate was then evaporated in vacuo and the residue was crystallized from ethanol to give 87mg (68%) of 61.

mp 253-254°C (dec.)
ir (HCl salt, KBr) cm\(^{-1}\): 3320 (NH), 1610 (aromatic)
nmr (CD\(_3\)OD) (ppm):
- 2.92-3.23 (m, 4H, ArCH\(_2\)CH\(_2\)N)
- 6.16 (s, 1H, ArH)
- 6.44 (s, 1H, ArCHN)
- 6.75 (s, 1H, ArH)
- 7.30-8.30 (m, 9H, 9xArH)

Analysis for C\(_{19}\)H\(_{17}\)NO\(_2\).HCl
Calculated: C, 69.62; H, 5.54; N, 4.27;
Found: C, 69.48; H, 5.66; N, 4.15.
**N-(3,4-dibenzoyloxyphenethyl)-5,6,7-trimethoxy-2-naphthylamide**

(86)

The amide 86 was prepared in a manner similar to described earlier for 85. Treatment of 1.1g (4.2mmole) of 5,6,7-trimethoxy-2 naphthoic acid with 1g (8mmole) of thionyl chloride provided the desired acid chloride that was allowed to react with 2.09 g (6.3 mmole) of 3,4-dibenzoyloxyphenethylamine (72) to give 1.7 g (70%) of amide 86.

mp 127-129°C

ir (neat) cm⁻¹: 3320(NH), 1645(C=O).

nmr (CDCl₃) (ppm):

2.87 (t, 2H, ArCH₂, J=6.7Hz)
3.50-3.75 (m, 2H, ArCH₂CH₂NH)
3.86 (s, 3H, 1xArOCH₃),
4.01 (s, 3H, 1xArOCH₃),
4.05 (s, 3H, 1xArOCH₃),
5.10 (s, 2H, ArCH₂O)
5.15 (s, 2H, ArCH₂O)
6.30 (br, 1H, NH)
6.65-7.15 (m, 3H, 3xArH)
7.20-8.20 (m, 14H, 14xArH)

Analysis for C_{36}H_{35}NO_6
Calculated: C, 74.85; H, 6.11; N, 2.42;
Found: C, 74.87; H, 6.29; N, 2.28.

1-(2'-(5',6',7'-trimethoxy) naphthyl)-6,7-dibenzyl oxy
-1,2,3,4 tetrahydroisoquinoline (88)

The tetrahydroisoquinoline 88 was prepared from 1.5g (2.6mmole) of the amide 87, 1.2g (7.8mmole) of phosphoryl chloride and 1.02g (26mmole) of sodium borohydride according to the procedure described for amide 86 to afford 1.12 g (72%) of 88 as HCl salt.

mp 224-225°C

ir (free base, neat) cm⁻¹: 3300(NH), 1630, 1610, 1580

nmr (CDCl₃) (ppm):
1.87 (s, 1H, NH)
2.10-2.70 (m, 4H, CH₂CH₂)
3.95 (s, 3H, 1xArOCH₃)
3.96 (s, 3H, 1xArOCH₃)
3.98 (s, 3H, 1xArOCH₃),
4.87 (s, 2H, ArCH₂O)
5.14 (s, 3H, ArCH₂O; and ArCHN)
6.36 (s, 1H, ArH)
6.74 (s, 1H, ArH)
6.88 (s, 1H, ArH)
7.10-8.10 (m, 13H, 13xArH)

Analysis for C₃₆H₃₅NO₅·HCl·0.1/2H₂O
Calculated: C, 71.22; H, 6.14; N, 2.30;
Found: C, 71.17; H, 6.24; N, 2.18.

1-(2-(5,6,7-trimethoxy)-naphthyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline (62)

![Chemical structure of 1-(2-(5,6,7-trimethoxy)-naphthyl-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline](image)

To a 50ml absolute ethanol solution of 400mg (0.67 mmole) the tetrahydroisoquinoline 88 was added 200 mg of 10% Pd/C and the mixture was hydrogenated at 40 psi at room temperature for 12 hours. After filtering through celite, the solvent was removed in vacuo. and the residue was crystallized from ethanol-ether to afford 213mg (76%) of the catechol 62.
mp 234-235°C (dec.)
ir (HCl salt, KBr) cm⁻¹: 3400-3200 (NH and OH)
nmr (CD₃OD) (ppm):
  2.96-3.80 (m, 4H, CH₂CH₂,
          overlapping with solvent peak)
  3.94 (s, 3H, 1xArOCH₃),
  3.96 (s, 3H, 1xArOCH₃),
  4.03 (s, 3H, 1xArOCH₃),
  5.68 (s, 1H, ArCHN)
  6.23 (s, 1H, ArH)
  6.72 (s, 1H, ArH)
  6.88 (s, 1H, ArH)
  7.11-8.14 (m, 3H, 3xArH)

Analysis for C₂₂H₂₃NO₅·HCl:
  Calculated: C, 63.23; H, 5.79; N, 3.35;
  Found: C, 63.02; H, 5.79; N, 3.26.

N-(3,4-dibenzylxyloxyphenethyl) – 3-(3',4',5'-trimethoxyphenyl)
propionamide (90)
A 250ml toluene solution of 9g (27mmole) 3,4-dibenzylxoyphenethylamine (72) and 6.5g (27mmole) of 3,4,5-trimethoxynphenyl propionic acid was heated at reflux for 48 hr with azeotropic removal of water using a Dean-Stark trap. The solution was then allowed to cool to room temperature and evaporated in vacuo. The residue was then taken into chloroform, washed with aqueous NaHCO₃, diluted HCl and dried (MgSO₄). The solvent was removed in vacuo and the residue was purified by column chromatography on silica gel using ethyl acetate as eluent. Recrystallization of the solid from ethyl acetate afforded 10.2g (68%) of the amide 90.

mp 91-92°C.

ir (neat)cm⁻¹: 3300(NH), 1635 (C=O)

nmr (CDCl₃) (ppm):

  2.71-2.96 (m, 6H, 3xCH₂)  
  3.31-3.57 (m, 2H, 1xCH₂)  
  3.81 (s, 9H, 3xArOCH₃)  
  5.13 (s, 4H, 2xArCH₂O)  
  5.29 (br, 1H, NH)  
  6.40 (s, 2H, 2xArH)  
  6.53-6.91 (m, 3H, 3xArH)  
  7.26-7.50 (m, 10H, 10xArH)

Analysis for C₃₄H₃₇NO₆

Calculated: C, 73.49; H, 6.71; N, 2.52;

Found: C, 73.62; H, 6.81; N, 2.46.
1-(3',4',5'-trimethoxyphenethyl) — 1,2,3,4-tetrahydro — 6,7 dibenzylxoy isoquinoline (91)

A 200ml acetonitrile solution of 3g (5.4mmole) of the amide 90 and 2.5g (16.2mmole) of phosphoryl chloride was allowed to reflux under argon for 2 hr. After the solvent was removed in vacuo the residue 2.5g (4.5 mmole) was taken into 100 ml of absolute methanol to which 1.71g (43.8 mmole) of sodium borohydride was added portionwise and allowed to stir at room temperature overnight. The solvent was removed in vacuo again and the residue was taken into chloroform and washed with aqueous NaHCO₃ and dried (MgSO₄) and evaporated again. The residue was purified by column chromatography on silica gel using 4.8% MeOH in chloroform with 1% NH₄OH as eluent. Preparation of the HCl salt from the free base gave 1.33 g(51%) of 91.

mp 112-114°C

ir (free base, neat) cm⁻¹: 3300(NH), 1595 (aromatic).

nmr (free base, CDCl₃) (ppm):
1.65-2.16 (m, 2H, CH₂CH₂CH)
2.55-3.30 (m, 6H, 3xCH₂)
3.83 (s, 3H, 1xArOCH₃)
3.84 (s, 6H, 2xArOCH$_3$)
3.90-4.15 (m, 1H, ArCHN)
5.09 (s, 2H, 1xArCH$_2$O)
5.13 (s, 2H, 1xArCH$_2$O)
6.42 (s, 2H, 2xArH)
6.68 (s, 2H, 2xArH)
7.20-7.50 (m, 10H, 10xArH)

m/e 539

Analysis for C$_{34}$H$_{38}$N$_1$O$_5$Cl$_1$.1/2H$_2$O:

Calculated: C, 69.48; H, 6.64; N, 2.38;

Found: C, 69.52; H, 6.77; N, 2.50.

1-(3',4',5'-trimethoxyphenethyl)-6,7-dihydroxy-1,2,3,4-
tetrahydroisoquinoline (63):

A 50ml MeOH suspension of 200mg of 10% Pd/C and 500mg
(0.87mmole) of the protected compound 91 was hydrogenated
at 40 psi on a Parr apparatus for 6 hr. The catalyst was
then removed by filtering through celite. The filtrate thus
collected was evaporated in vacuo and the residue was triturated
in ether to afford a white solid which was crystallized from absolute ethanol to give 180mg (52%) of 63.
mp 218-220°C

ir (HCl salt, KBr) cm⁻¹: 3410 to 3205 (br, OH and NH)

nmr (HCl salt, CD₃OD) (ppm):
2.10-2.40 (m, 2H, CH₂CH₂CH)
2.65-3.70 (m, 6H, 3xCH₂)
3.73 (s, 3H, 1xAroCH₃)
3.84 (s, 6H, 2xAroCH₃)
4.40 (t, 1H, ArCHN, J=6.5Hz)
6.58 (s, 2H, 2xArH)
6.63 (s, 1H, 1xArH)
6.65 (s, 1H, 1xArH)

m/e 359

Analysis for C₂₀H₂₅N₁O₅.HCl.2H₂O:
Calculated: C, 55.68; H, 6.90; N, 3.24;
Found: C, 55.71; H, 6.80; N, 3.23.

3-(3',4'-methylenedioxyphenyl)propionic acid (93)

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

93

The acid 93 was prepared from 3,4-methylenedioxy cinnamic acid(22) by using the procedure described by Haworth, Perkin and Robinson(14) A 500 ml aqueous solution containing
11.2g (0.2mole) of potassium hydroxide and 38.4g (0.2mole) of acid 92 was added dropwise to vigorously stirring 2% sodium amalgam (570g). After the addition was complete, the mixture was allowed to stir at room temperature for another hour. The aqueous layer was separated and acidified with diluted HCl. The precipitated acid 93 was collected and recrystallized from methanol to afford 32.8g (85%) of the acid 93.

mp 87-88°C (Lit.114 87-88°C).

ir (KBr) cm⁻¹: 1690 (C=O)

nmr (CDCl₃) (ppm):

2.40-3.00 (m, 4H, ArCH₂CH₂)
5.83 (s, 2H, OCH₂O)
6.61 (s, 3H, 3xArH)
9.35 (br, 1H, COOH)

3-(3',4'-Methylenedioxyphenyl)-propionamide(94)

To a 25 ml chloroform solution of 2.16g (20mmole) of ethyl chloroformate was added dropwise 25ml chloroform solution of 3.84g (20mmole) of acid 93 and 2.04g (20mmole) of
triethylamine at 0°C. The mixture was allowed to stir for another hour and cooled with an acetone-dry ice bath. To the cooled solution, 5ml (50mmole) of liquid ammonia was collected and the mixture was allowed to stir for 30 minutes. The precipitate thus formed was filtered and the filtrate was washed with aqueous NaHCO₃ and dried (MgSO₄). The solvent was removed in vacuo and the solid thus formed was recrystallized from methanol to give 3.11g (82%) of the amide 94.

mp :121-122°C (Lit.114 123°C).

ir (KBr)cm⁻¹: 3390 (NH), 1640 (C=O)

nmr (CDCl₃) (ppm):

2.12-2.92 (m, 4H, ArCH₂CH₂)
5.85 (s, 2H, OCH₂O)
6.61 (s, 3H, 3xArH)
7.06 (br, 2H, NH₂)

3-(3',4'-methylenedioxyphenyl)propylamine (95).

![Chemical structure](image)

To a 25 ml THF solution of 2.13g (11mmole) of the amide 94 was added dropwise 20ml of 1M diborane in THF solution
under argon atmosphere at 0°C. When the addition was completed, the mixture was allowed to heat at reflux for 6 hr then allowed to cool to 0°C and 15 ml of absolute methanol was added to quench the reaction. The mixture was then evaporated in vacuo. This process was repeated for 4 times and the residue thus formed was taken into chloroform and treated with dry HCl, then washed with aqueous NaHCO₃ and dried (MgSO₄). The chloroform solution was then treated with dry HCl again and the HCl salt was crystallized from chloroform-hexane to give 1.2g (56%) of amine 95.

mp 211-212°C (Lit.116 206-208°C).

ir (KBr) cm⁻¹: 3400 (NH₂)

nmr (CDCl₃) (ppm):

2.22 (s, 2H, NH₂)
2.33-2.83 (m, 4H, ArCH₂CH₂)
5.85 (s, 2H, OCH₂O)
6.58 (s, 3H, 3xArH)

N-(3',4'-methylenedioxyphenyl)propyl-3,4,5-trimethoxyphenyl acetamide (96)
The synthetic procedure for the amide 96 is the same as described for amide 73 by using 0.56g(2.5mmole) of 3',4',5'-trimethoxy phenylacetic acid, 0.3g(2.5mmole) of thionyl chloride and 0.45g (2.5mmole) of the amine 72 to give 0.56g (57.6%) of the amide 96.

mp 103-104°C

ir (neat)cm⁻¹: 3290(NH), 1635 (C=O).

nmr (CDCl₃) (ppm):
1.73 (m, 2H, ArCH₂CH₂CH₂)
2.50 (m, 2H, ArCH₂CH₂CH₂)
3.23 (m, 2H, CH₂NH)
3.48 (s, 2H, ArCH₂CO)
3.83 (s, 9H, 3xArOCH₃),
5.47 (br, 1H, NH)
5.90 (s, 2H, OCH₂O)
6.48 (s, 2H, 2xArH)
6.54-6.70 (m, 3H, 3xArH)

Analysis for C₂₁H₂₅NO₆:

Calculated: C, 65.10; H, 6.50; N, 3.62;

Found: C, 65.26; H, 6.79; N, 3.68.
1-(3',4',5'-Trimethoxybenzyl)-7,8-methylenedioxy
2,3,4,5-tetrahydro-1H-2-benzazepine (97)

A 50ml dry acetonitrile solution of 1.94g (5mmole) of the amide 96 and 2.3g (15mmole) of phosphoryl chloride was heated under bubbling argon at a 95°C oil bath for 5 hr. The mixture was allowed to come to room temperature and the solvent was evaporated in vacuo. The residue was dissolved directly into 50ml of dry THF and allowed to cool to 0°C and to which 100ml of 1M diborane in THF solution was added. The mixture was allowed to heat at reflux for 9 hr and allowed to cool to 0°C again. To the cooled mixture, 5ml of absolute methanol was added to quench the reaction. The solvent was evaporated in vacuo and this process was repeated 4 times. The residue thus formed was purified by column chromatography on silica gel using 5% methanol in chloroform (with 1% of NH₄OH) as eluent to afford 185mg (15%) of the tetrahydrobenzazepine 97 as an oil which solidified upon standing and recrystallized from methanol.

mp 128-128.5°C
ir (free base, neat) : 3400(NH), 1590 (aromatic).
nmr (free base, CDCl₃) (ppm):
1.50-1.73 (m, 3H, ArCH₂CH₂CH₂ and NH)
2.65-3.40 (m, 6H, ArCH₂CH₂CH₂ and ArCH₂CHN)
3.85 (s, 9H, 3xArOCH₃),
5.90 (s, 2H, OCH₂O)
6.47 (s, 2H, 2xArH)
6.66 (s, 1H, 1xArH)
6.74 (s, 1H, 1xArH)
m/e EI: 190 (100%), 181 (12.3%); CI (isobutane): 372 (M+1)

Analysis for C₂₁H₂₅N₂O₅:
Calculated: C, 67.90; H, 6.78; N, 3.77;
Found: C, 67.97; H, 6.83; N, 3.70.

Boron trichloride reaction with 1-(3',4',5'-trimethoxybenzyl)
7,8-methylenedioxy-2,3,4,5-tetrahydro-1H-2-benzazepine (97)

To a 5ml methylene chloride solution of 37.1mg (0.1mmole) of 97 was added 0.2ml (0.2mmole) of 1M methylene chloride solution of boron trichloride at 0°C under argon atmosphere. The mixture was then allowed to stir for 5hr and 0.2ml of absolute methanol was added to quench the reaction. After stirring for another hour the mixture was evaporated in vacuo and the residue was crystallized from ethanol-ether to give 17mg (43%) of the catechol 64. The NMR spectrum matched with that of catechol 64 from catalytic hydrogenation. Thin layer chromatography on silica gel using ethylacetate:acetic acid:water=6:3:1 as eluent also indicated a matched spot with catechol 64 with a Rf value of 0.30.
3-(3',4'-dibenzylxyphenyl)propionic acid (99)

A mixture of 7.2g (40mmole) of 3,4-dihydroxy dihydrocinnamic acid, 7.6g (60mmole) benzyl chloride and 8.3g of potassium carbonate and 150ml of methanol was heated at reflux for 12 hr. To the mixture was added a 5ml aqueous solution containing 3.36g (60mmole) of potassium hydroxide and heated at reflux for another 4 hr. After allowing to come to room temperature, the mixture was extracted with ether. The aqueous layer was acidified with diluted HCl. The precipitate thus formed was collected and was recrystallized from methanol to give 8g (68%) of the acid 99.

mp :116-117°C (Lit. 116-117°C).

ir (KBr)cm⁻¹: 1710 (C=O)

nmr (CDCl₃) (ppm):
2.30-3.05 (m, 4H, ArCH₂CH₂)
5.01 (s, 4H, 2xArCH₂O)
6.44-6.90 (m, 3H, 3xArH)
7.00-7.50 (m, 10H, 10xArH)
8.35 (br, 1H, COOH)
3-(3',4'-dibenzylxoyphenyl)propionamide (100)

The synthetic procedure for amide 100 is the same as the synthetic procedure for the amide 94 using 20g (56mmole) of the acid 99 and 6.1g (56mmole) of ethyl chloroformate, 5.2g (56mmole) of triethylamine and 50ml of liquid ammonia to give 15.6g (77%) of the amide 100.

mp: 126°C (Lit 142-26°C).

ir (KBr) cm⁻¹: 3400(NH), 1655 (C=O)

nmr (CDCl₃) (ppm):
2.00-3.00 (m, 4H, ArCH₂CH₂)
5.03 (s, 4H, 2xArCH₂O)
5.45 (br, 2H, CONH₂)
6.40-6.90 (m, 3H, 3xArH)
7.00-7.50 (m, 10H, 10xArH)
3-(3',4'-dibenzoyloxyphenyl)propylamine (101)

The synthetic procedure for amine 101 is the same as the synthetic procedure for the amine 95 using 7.2g (73.3mmole) of the amide 100 and 280ml of 1M solution of diborane in THF to afford 4.84g (63%) of the amine 101 as the HCl salt.

mp 100-102°C

ir (free base, neat) cm⁻¹: 3360(NH)

nmr (HCl salt, CDCl₃) (ppm):

1.44 (s, 3H, NH₃)
1.60-1.84 (m, 2H, ArCH₂CH₂CH₂NH)
2.56 (t, 2H, ArCH₂CH₂CH₂N, J=8Hz)
2.67 (t, 2H, ArCH₂, J=7Hz)
5.13 (s, 2H, ArCH₂O)
5.15 (s, 2H, ArCH₂O)
6.74-6.92 (m, 3H, 3xArH)
7.29-7.40 (m, 10H, 10xArH)

Analysis for C₂₃H₂₅N₁O₂·HCl

Calculated: C, 71.95; H, 6.83; N, 3.65;

Found: C, 72.08; H, 6.93; N, 3.65.
N-(3',4'-dibenzylxyloxyphenylpropyl)-3,4,5-trimethoxyphenyl acetamide (103)

The synthetic procedure for amide 103 is the same as that for amide 96 using 2.3g (7.8mmole) of 3,4,5-trimethoxyphenyl acetic acid and 2.7g (7.8mmole) of the amine 101 to afford 2.7g (61%) of the amide 103.

mp 100–102°C

ir (KBr) cm⁻¹: 3310(NH), 1640 (C=O)
nmr (CDCl₃) (ppm):
- 1.74 (m, 2H, ArCH₂CH₂CH₂NH)
- 2.48 (t, 2H, ArCH₂CH₂CH₂N)
- 3.18 (m, 2H, CH₂NH)
- 3.46 (s, 2H, ArCH₂CO)
- 3.83 (s, 9H, 3xAroCH₃)
- 5.12 (s, 4H, 2xArCH₂O)
- 5.45 (br, 1H, NH)
- 6.44 (s, 2H, 2xArH)
- 6.51–6.92 (m, 3H, 3xArH)
- 7.30–7.50 (m, 10H, 10xArH)
m/e (EI): 555

Analysis for C_{34}H_{37}N_{10}O_6

Calculated: C, 73.49; H, 6.71; N, 2.52;

Found: C, 73.47; H, 6.66; N, 2.48.

1-(3',4',5'-trimethoxybenzyl)-7,8-dibenzylxyo-2,3,4,5-tetrahydro-1H-2-benzazepine (104)

The synthetic procedure for tetrahydrobenzazepine 104 is the same as the synthetic procedure for tetrahydrobenzazepine 97 using 2.12g (3.8mmole) of the amide 103, 1.76g (11.5mmole) of phosphoryl chloride and 60ml of 1M solution of diborane in THF to afford 0.78g of the tetrahydrobenzazepine 104 as HCl salt which was recrystallized from absolute ethanol. (58% yield)

mp 91.5-93°C

ir (free base, neat) cm⁻¹: 3320(NH), 1595 (aromatic)

nmr (free base, CDCl₃) (ppm):

1.70 (m, 2H, ArCH₂CH₂CH₂NH)
2.20 (br, 1H, NH)
2.40-3.35 (m, 6H, ArCH₂CH₂CH₂N and ArCH₂CHN)
3.82 (s, 6H, 2xArOCH₃)
3.84 (s, 3H, 1xArOCH<sub>3</sub>)
4.04 (dd, 1H, ArCHN, J=9.3Hz, 5.3Hz)
5.06 (s, 2H, 1xArCH<sub>2</sub>O)
5.12 (s, 2H, 1xArCH<sub>2</sub>O)
6.42 (s, 2H, 2xArH)
6.78 (s, 1H, 1xArH)
6.80 (s, 1H, 1xArH)
7.23-7.55 (m, 10H, 10xArH)

m/e (EI): 539(1.2%), 358(77.8%)

Analysis for C<sub>34</sub>H<sub>37</sub>N<sub>1</sub>O<sub>5</sub>·HCl

Calculated: C, 70.88; H, 6.65; N, 2.43;
Found: C, 70.61; H, 6.80; N, 2.39.

1-(3',4',5'-trimethoxybenzyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1H-2-benzazepine (64)

To a 50ml ethanol solution of 300mg (0.5mmole) of 104 was added 300mg of 10% Pd/C and the mixture was hydrogenated at 40 psi at room temperature overnight. The catalyst was then removed by filtration through celite and the filtrate was evaporated in vacuo. The residue thus formed was crystal-
lized from ethanol-ether and recrystallized from ethanol to give 154 mg (75%) of the catechol.

mp  195-196°C

ir (HCl salt, KBr) cm⁻¹: 3200 (NH), 1595 (aromatic)

nmr (HCl salt, CD₃OD) (ppm):

1.90 (m, 2H, ArCH₂CH₂CH₂NH)
2.90-3.60 (m, 6H, ArCH₂CH₂CH₂N and ArCH₂CHN)
3.72 (s, 3H, 1xArOCH₃)
3.76 (s, 6H, 2xArOCH₃)
4.60 (m, 1H, ArCHN)
6.44 (s, 2H, 2xArH)
6.53 (s, 1H, 1xArH)
6.70 (s, 1H, 1xArH)

m/e (EI): 359 (15.5%), 178 (100%)

Analysis for C₂₀H₂₅N₁O₅·HCl

Calculated: C, 60.68; H, 6.62; N, 3.53;
Found: C, 60.50; H, 6.78; N, 3.49.

2-Benzyl-1-(3',4',5'-trimethoxybenzoyl)-6,7-dibenzylxyloxy-3,4-dihydroisoquinoline bromide (112)
The dihydroisoquinoline free base of 112 was prepared according to the procedure described by Miller et al. A 100ml dry acetonitrile solution of 5.41g (1mmole) of N-(3'4'-dibenzoloxyphenyl)-3',4',5'-trimethoxyphenylacetamide and 4.6g (3mmole) of phosphoryl chloride was heated at reflux under argon atmosphere for 3 hr. The solvent was removed in vacuo and the residue was dissolved in chloroform and washed with aqueous NaHCO₃. The chloroform layer was dried (MgSO₄) and evaporated in vacuo. The residue was dissolved in 100ml of toluene and divided into five aliquots. Each aliquot of toluene solution was allowed to heat at a 100°C oil bath in the open air with vigorous stirring for 15 minutes. After allowing to come to room temperature, hexane was added until cloudiness occurred. The mixtures were allowed to stand overnight and the crude dihydroisoquinoline free base of 112 was collected and recrystallized from methanol to afford 4.3g (80%) of the free base.

mp : 145-147°C (Lit. 100 147-150°C).

ir (free base, KBr) cm⁻¹: 1670(C=O)

nmr (free base, CDCl₃) (ppm):

2.74-2.88 (m, 2H, ArCH₂CH₂N)
3.75-4.05 (m, 2H, ArCH₂CH₂N, overlapped with ArOCH₃ peaks)
3.86 (s, 6H, 2xArOCH₃)
3.93 (s, 3H, 1xArOCH₃)
5.05 (s, 2H, 1xArCH₂O)
5.22 (s, 2H, 1xArCH₂O)
6.80 (s, 1H, 1xArH)
7.00 (s, 1H, 1xArH)
7.16-7.52 (m, 12H, 12xArH)

The benzyl bromide salt of the dihydroisoquinoline 112 was prepared according to the procedure described by Schmidhammer95. A 50ml dry benzene solution of 2.23g (4.15mmole) of the free base of 112 and 1.42g (8.30mmole) of benzyl bromide was heated at reflux under argon atmosphere overnight. After allowing to come to room temperature, the solvent was removed in vacuo. The residue thus formed was washed with dry ether and the resulting solid was collected and recrystallized from ethanol to give 2.28g (78%) of 112.

mp .:148-151 °C (Lit.95 145-150°C).
ir (KBr)om̅̅^{-1}: 1665(C=O)
nmrm(CDC1₃)(ppm):
2.70-3.00 (m, 4H,rCH₂CH₂N)
4.02 (s, 9H, 3xArOCH₃)
4.97 (s, 2H, 1xArCH₂N)
5.04 (s, 2H, 1xArCH₂O)
5.30 (s, 2H, 1xArCH₂O)
6.71 (s, 1H, 1xArH)
6.92 (s, 1H, 1xArH)
7.00-7.60 (m, 17H, 17xArH)
1- and 2-(3',4',5'-Trimethoxybenzoyl)-4,5-dihydro-7,8-dibenzoyloxy-3-benzyl-3H-3-benzazepine (113) and (114)

The two isomeric dihydrobenzazepines 113 and 114 were prepared according to the procedure described by Kametani et al.\textsuperscript{122,138}. To a methylene chloride solution of 2.2g (3.1mmole) of the benzyl bromide salt 112 was added an ether solution of approximate 1.2g (28.5mmole) of diazomethane (generated from 8.6g of Diazald) at 0°C. The mixture was allowed to stand for 3 hr and the solvent was removed \textit{in vacuo}. The residue was dissolved in chloroform and washed with 10% of ammonia water. The chloroform layer was dried (\textit{MgSO}_4) and evaporated \textit{in vacuo} again. The residue was purified by column chromatography on silica gel using 10% ether in chloroform (with 1% \textit{NH}_4\textit{OH}) as eluent to afford 0.59g (29%) of the 1-benzoyl isomer 113 and 0.67g (33%) of the 2-benzoyl isomer 114.

for the 1-benzoyl isomer 113:

mp 120-120.5°C

ir (free base, neat) cm\(^{-1}\): 1640 (C=O), 1580 (aromatic)

nmr (free base, CDCl\(_3\)) (ppm):
2.32-3.02 and 3.38-3.58 (each m, each 2H, ArCH₂CH₂N)
3.75 (s, 6H, 2xArOCH₃)
3.85 (s, 3H, 1xArOCH₃)
4.37 (s, 2H, ArCH₂N)
4.87 (s, 2H, ArCH₂O)
5.09 (s, 2H, ArCH₂O)
6.58 (s, 1H, =C-H)
6.82 (s, 2H, 2xArH)
6.93 (s, 1H, 1xArH)
7.10-7.50 (m, 15H, 15xArH)
6.78 (s, 1H, 1xArH)

m/e (EI): 641

Analysis for C₄₁H₃₉N₁O₆
Calculated: C, 76.73; H, 6.13; N, 2.18;
           Found:  C, 76.91; H, 6.25; N, 2.23.

for the 2-benzoyl isomer: 114:

mp  102-104.5°C

ir (free base, neat) cm⁻¹: 1655 (C=O), 1610, 1590 (aromatic)

nmr (free base, CDCl₃) (ppm):
2.72-2.92 and 3.08-3.28 (each m, each 2H, ArCH₂CH₂N)
3.85 (s, 6H, 2xArOCH₃)
3.94 (s, 3H, 1xArOCH₃)
4.04 (s, 2H, ArCH₂N)
5.10 (s, 2H, ArCH₂O)
5.13 (s, 2H, ArCH₂O)
5.93 (s, 1H, =C-H)
6.72 (s, 2H, 2xArH)
6.80 (s, 1H, 1xArH)
7.21 (s, 1H, 1xArH)
7.20-7.50 (m, 15H, 15xArH)

m/e (EI): 641

Analysis for C₄₁H₃₉N₁O₆

Calculated: C, 76.73; H, 6.13; N, 2.18;

Found: C, 76.94; H, 6.25; N, 2.18.

1-(3', 4', 5'-trimethoxybenzoyl)-7, 8-dibenzylxoy-3-benzyl-2, 3, 4, 5- tetrahydro-1H-3-benzazepine (118)

To a 5 ml trifluoroacetic acid solution of 196mg (0.3mmole) of the 1-benzoyl dihydrobenzazepine was added dropwise a 6ml solution of 1M diborane in THF under argon atmosphere at 0°C. After the addition was complete the mixture was allowed to stir until bubbling ceased. To the mixture 10ml of water was added to quench the reaction and the mixture was allowed to stir again until bubbling ceased. The organic layer was separated and evaporated in vacuo and the residue was then dissolved in 10ml of chloroform and washed with aqueous NaHCO₃ and dried (MgSO₄). The chloro-
form solution thus formed was evaporated \textit{in vacuo} again to

give a yellowish residue which was purified by column chro-

matography on silica gel using 10% ether in chloroform (with

1% NH\textsubscript{4}OH) as eluent to afford 189mg (96%) of 118.

mp 119-121^\circ C

ir (free base, neat) cm\textsuperscript{-1}: 1680 (C=O)

nmr (free base, CDCl\textsubscript{3}) (ppm):

- 2.23-3.81 (m, 6H, ArCH\textsubscript{2}CH\textsubscript{2}N and ArCHCH\textsubscript{2}N)
- 3.42 (d, 1H, 1/2ArCH\textsubscript{2}N, J=13Hz)
- 3.64 (d, 1H, 1/2ArCH\textsubscript{2}N, J=13Hz)
- 3.76 (s, 6H, 2xArOCH\textsubscript{3})
- 3.91 (s, 3H, 1xArOCH\textsubscript{3})
- 4.72 (m, 1H, ArCHCH\textsubscript{2})
- 4.92 (d, 1H, 1/2xArCH\textsubscript{2}O, J=12.6Hz)
- 5.00 (d, 1H, 1/2xArCH\textsubscript{2}O, J=12.6Hz)
- 5.11 (s, 2H, ArCH\textsubscript{2}O)
- 6.50 (s, 1H, 1xArH)
- 6.78 (s, 1H, 1xArH)
- 7.04 (s, 2H, 2xArH)
- 7.18-7.60 (m, 15H, 15xArH)

m/e (EI): 643

Analysis for C\textsubscript{41}H\textsubscript{41}N\textsubscript{1}O\textsubscript{6}

Calculated: C, 76.49; H, 6.42; N, 2.18;

Found: C, 76.57; H, 6.56; N, 2.16.
1-(α-Hydroxy-3',4',5'-trimethoxybenzyl)-7,8-dibenzyl-3-benzyl-2,3,4,5-tetrahydro-1H-3-benzazepine (119)

To a 20ml absolute ethanol solution of 480mg (0.75mmole) of the 1-benzoyl tetrahydrobenzazepine 118 was added 567mg (15mmole) of sodium borohydride and the mixture was allowed to heat at reflux for 2 hr. After the mixture was allowed to come to room temperature, the solvent was removed in vacuo and the residue was taken into 20ml of chloroform and washed with aqueous NaHCO₃, dried (MgSO₄) and the solvent was removed in vacuo again. The residue thus formed was purified by column chromatography on silica gel using 10% ether in chloroform (with 1% NH₄OH) as eluent to give the free base from which the HCl salt was prepared and was recrystallized from absolute ethanol to give 500mg (97.8%) of 119 as the HCl salt.

mp 168-170°C

ir (free base, neat)cm⁻¹: 3300 (OH), 1600 (aromatic)

nmr (free base, CDCl₃) (ppm):

3.10-4.00 (m, 9H, ArCH₂CH₂N and ArCH₂N

and ArCHCH₂N)
3.67 (s, 6H, 2xArOCH₃)
3.75 (s, 3H, 1xArOCH₃)
4.66 (d, 1H, 1/2xArCH₂O, J=12.1Hz)
4.72 (d, 1H, 1/2xArCH₂O, J=12.1Hz)
5.08 (s, 2H, ArCH₂O)
5.15 (d, 1H, ArCHOH, J=4.1Hz)
5.99 (s, 1H, 1xArH)
6.32 (s, 2H, 2xArH)
6.69 (s, 1H, 1xArH)
7.10-7.50 (m, 15H, 15xArH)

m/e (EI): 645

Analysis for C₄₁H₴₃N₈O₆.HCl.H₂O:
Calculated: C,70.32; H,6.62; N,2.00;
Found: C,70.74; H,6.58; N,2.05.

1-(3',4',5'-trimethoxybenzylidenyl)-7,8-dibenzoyloxy-3-benzyl-2,3,4,5-tetrahydro-1H-3-benzazepine (120)

To a 50ml benzene solution of 125mg (0.184mmole) of the 1-α-hydroxybenzyl tetrahydrobenzazepine 119 was added 70mg (0.367mmole) of p-toluene sulfonic acid and the mixture was
allowed to heat in a 80°C oil bath overnight. The solvent was then evaporated in vacuo and the residue was taken into chloroform and washed with aqueous NaHCO₃ and dried (MgSO₄) and evaporated in vacuo again. The free base was crystallized from ethanol afforded 106mg (91.8%) of 120.

mp 135-136°C (free base).

ir (free base, neat) cm⁻¹: 1605 (aromatic)

nmr (free base, CDCl₃) (ppm):

  2.73-3.03 (m, 4H, ArCH₂CH₂N)
  3.37 (s, 2H, ArCCH₂N)
  3.55 (s, 6H, 2xArOCH₃)
  3.80 (s, 3H, 1xArOCH₃)
  3.83 (s, 2H, ArCH₂N)
  4.87 (s, 2H, ArCH₂O)
  5.15 (s, 2H, ArCH₂O)
  6.22 (s, 2H, 2xArH)
  6.36 (s, 1H, =CH⁻)
  6.62 (s, 1H, 1xArH)
  6.80 (s, 1H, 1xArH)
  7.20-7.55 (m, 15H, 15xArH)

Analysis for C₄₁H₄₁N₁O₅·H₂O:
Calculated: C, 76.26; H, 6.71; N, 2.17;
Found: C, 75.91; H, 6.57; N, 2.10.
1-(3',4',5'-trimethoxybenzyl)-7,8-dihydroxy-2,3,4,5-tetrahydro-1 H-3-benzazepine (65)

![Chemical Structure](image)

To a 50ml absolute ethanol solution of 150mg (0.22mmole) of the 1-benzylidenyl tetrahydrobenzazepine 120 was added 75mg of 10%Pd/C and the mixture was hydrogenated at 40 psi overnight. The mixture was filtered through celite and the filtrate was evaporated in vacuo. The residue thus formed was triturated in ether and the solid was crystallized from ethanol-ether to give 70mg (77%) of catechol 65 as HCl salt.

- **mp**: 150-152°C
- **ir** (HCl salt, KBr) cm⁻¹: 3160(OH), 1594 (aromatic)
- **nmr** (HCl salt, CD₃OD) (ppm):
  - 2.65-3.15 (m, 9H, ArCH₂CH₂N and ArCH₂CH₂)
  - 3.72 (s, 6H, 2xArOCH₃)
  - 3.77 (s, 3H, 1xArOCH₃)
  - 6.42 (s, 2H, 2xArH)
  - 6.52 (s, 1H, 1xArH)
  - 6.66 (s, 1H, 1xArH)

- **m/e (EI)**: 359(10.6%), 178(100%)
Analysis for C$_{20}$H$_{25}$N$_{1}$O$_{5}$·HCl·3/4H$_{2}$O:
Calculated: C, 58.68; H, 6.77; N, 3.42;
Found: C, 58.74; H, 6.87; N, 3.23.

2-(3', 4', 5'-trimethoxybenzoyl)-7, 8-dibenzyloxy-3-benzyl-
2, 3, 4, 5-tetrahydro-1H-3-benzazepine (121)

The synthetic procedure for the 2-benzoyl tetrahydrobenz-
azepine 121 is the same as that described for 118 using
513mg (0.8mmole) of the 2-benzoyl dihydrobenzazepine 114
and 20ml of 1M diborane in THF solution to afford 500mg
(92%) of 121 as HCl salt.

mp 177-179°C

ir (free base, neat) cm$^{-1}$: 1676 (C=O)

nmr (free base, CDCl$_3$) (ppm):
2.50-3.70 (m, 6H, ArCH$_2$CH$_2$N and ArCH$_2$CHCO)
3.85 (s, 6H, 2xArOCH$_3$)
3.94 (s, 3H, 1xArOCH$_3$)
3.78-4.15 (q, 2H, ArCH$_2$N)
4.30 (d, 1H, ArCH$_2$CHO, J=7.3Hz)
5.01 (s, 2H, ArCH$_2$O)
5.11 (s, 1H, ArCH$_2$O)
6.56 (s, 1H, 1xArH)
6.74 (s, 1H, 1xArH)
7.15-7.65 (m, 17H, 17xArH)

m/e (EI): 643

Analysis for C_{41}H_{41}N_1O_6-HCl:

Calculated: C, 72.39; H, 6.22; N, 2.06;
Found: C, 72.10; H, 6.31; N, 2.01.

2-(α-Hydroxy-3',4',5'-trimethoxybenzyl)-7,8-dibenzylloxy 3-benzyl-2,3,4,5-tetrahydro-1H-3-benzazepine (122)

The 2-(α-hydroxybenzyl) tetrahydrobenzazepine 122 was prepared from 230mg (0.34mmole) of the 2-benzoyl tetrahydrobenzazepine 121 and 132mg of sodium borohydride using the same procedure as described for 119 to give 214mg (92.3%) of 122 as HCl salt.

mp 135-137°C

ir (free base, neat)cm⁻¹: 3360 (OH), 1600 (aromatic)

nmr (free base, CDCl₃) (ppm):
0.70-1.30, 1.90-2.40 and 2.70-3.80
(m, 7H, ArCH₂CH₂N and ArCH₂CHN)
3.68 (s, 6H, 2xArOCH₃)
3.75 (s, 3H, 1xArOCH₃)
3.86-4.30 (m, 3H, ArCHOH and ArCH₂N)
4.92 (s, 2H, ArCH₂O)
5.03 (s, 2H, ArCH₂O)
6.29 (s, 2H, 2xArH)
6.39 (s, 1H, 1xArH)
6.64 (s, 1H, 1xArH)
7.00-7.45 (m, 15H, 15xArH)

m/e (EI): 645

Analysis for C₄₁H₄₃N₁O₆·HCl·3/4H₂O:
  Calculated: C, 70.78; H, 6.59; N, 2.01;
  Found: C, 70.88; H, 6.71; N, 2.04.

2-(3',4',5'-Trimethoxybenzyl)-7,8-dibenzylxyloxy-3-benzyl-
2,3,4,5-tetrahydro-1H-3-benzazepine(123)

To a 20ml dichloromethane solution of 200mg (0.29mmole)
of the 2-(α-hydroxybenzyl)tetrahydrobenzazepine122 was added
5ml (1.47mmole) of thionyl chloride at 0°C under argon atmo-
sphere. The mixture was allowed to stir overnight and the solvent was removed in vacuo. The residue was dissolved in 20ml of dry THF and allowed to cool to 0°C. To the solution was added 532mg (14 mmole) of lithium aluminum hydride and the mixture was heated to reflux under argon atmosphere overnight. After the mixture was allowed to cool to 0°C, 500mg of Na₂SO₄·10H₂O crystals was added and allowed to stir for 2hr. The white precipitate thus formed was filtered and the filtrate was evaporated in vacuo. From the residue the HCl salt was prepared and recrystallized from absolute ethanol to give 100mg (51.2%) of 123.

mp 128-130°C

ir (free base, neat) cm⁻¹: 1590 (aromatic).

nmr (free base, CDCl₃) (ppm):
2.25-3.37 (m, 9H, ArCH₂CH₂N
and ArCH₂CHCH₂Ar)
3.74 (s, 6H, 2xArOCH₃)
3.83 (s, 3H, 1xArOCH₃)
3.90 (s, 2H, ArCH₂N)
5.04 (s, 2H, ArCH₂O)
5.12 (s, 2H, ArCH₂O)
6.18 (s, 2H, 2xArH)
6.58 (s, 1H, 1xArH)
6.75 (s, 1H, 1xArH)
7.18-7.58 (m, 15H, 15xArH)

Analysis for C₄₁H₄₃N·0.₅·HCl
Calculated: C, 73.91; H, 6.66; N, 2.10;
Found: C, 73.74; H, 6.82; N, 2.01.

2-(3', 4', 5'-trimethoxybenzyl)-7, 8-dihydroxy-2, 3, 4, 5-tetrahydro-1H-3-benzazepine HCl (66):

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

To a 75ml absolute ethanol solution of 200mg (0.3mmole) of the 2-benzyl tetrahydrobenzazepine HCl salt 123 was added 100mg of 10%Pd/C and the mixture was hydrogenated at 40 psi overnight. The catalyst was then removed by filtration through celite and the filtrate was evaporated in vacuo. The residue thus formed was crystallized from ethanol-ether to afford 73mg (61.4%) of the catechol 66 as HCl salt.

mp 147-150°C

ir (HCl salt, KBr) cm\(^{-1}\): 3400-3200 (OH and NH)
nmr (HCl salt, CD\(_3\)OD) (ppm):

2.25-3.00 (m, 9H, ArCH\(_2\)CH\(_2\)N and ArCH\(_2\)CHCH\(_2\)Ar)
3.78 (s, 3H, 1xArOCH\(_3\))
3.85 (s, 6H, 2xArOCH\(_3\))
6.42 (s, 1H, 1xArH)
6.54 (s, 2H, 2xArH)
6.64 (s, 1H, 1xArH)
m/e (EI): 359 (1%), 178 (100%)

Analysis for C_{20}H_{25}N_{1.5}O_{5}.HCl.3/2H_{2}O
Calculated: C, 56.80; H, 6.91; N, 3.31;
Found: C, 55.69; H, 7.10; N, 3.13.

N-(3',4'-methylenedioxyphenyl)ethyl-3,4,5-trimethoxy phenylacetamide (126).

The synthetic procedure for amide 126 is the same as that described for amide 96 using 7g (42.5mmole) of 3,4-methylenedioxyphenyl ethylamine\(^{144}\) and 9.6g (42.5mmole) of 3,4,5-trimethoxyphenylacetic acid to afford 13g (82%) of the amide 126.

mp 105-106 °C
ir (KBr) cm\(^{-1}\): 1640.
nmr (CDCl\(_3\)) (ppm):
- 2.65 (t, 2H, ArCH\(_2\)CH\(_2\)N)
- 3.25-3.55 (m, 4H, CH\(_2\) and ArCH\(_2\)CO)
- 3.82 (s, 6H, 2xArOCH\(_3\))
- 3.83 (s, 3H, 1xArOCH\(_3\))
- 5.44 (br, 1H, NH)
5.91 (s, 2H, OCH₂O)
6.38 (s, 2H, 2xArH)
6.40-6.75 (m, 3H, 3xArH)

Analysis for C₂₀H₂₃N₁O₆
Calculated: C, 64.33; H, 6.21; N, 3.75.
Found: C, 64.54; H, 6.31; N, 3.72.

2-Benzyl-1-(3',4',5'-trimethoxybenzoyl) – 6,7-methylenedioxy
3,4-dihydroisoquinoline bromide (127)

The free base of the dihydroisoquinoline 127 was prepared
from 7.46g (20mmole) of N-(3',4'-methylenedioxyphenyl)-3,4,5-trimethoxyphenylacetamide (126) according to the
procedure described for the dihydroisoquinoline that served
as a precursor for 112 to afford the free base 3.6g (50%).

mp 153-154°C
ir (free base, KBr) cm⁻¹: 1660 (C=O).

nmr (free base, CDCl₃) (ppm):
2.77 (t, 2H, CH₂)
3.74-4.05 (m, 2H, CH₂)
3.88 (s, 6H, 2xArOCH₃)
3.92 (s, 3H, 1xArOCH₃)
5.97 (s, 2H, OCH₂O)
6.73 (s, 1H, 1xArH)
6.83 (s, 1H, 1xArH)
7.28 (s, 2H, 2xArH)

Analysis for C₂₀H₁₉N₁O₆:
Calculated: C, 65.04; H, 5.18; N, 3.79;
Found: C, 64.89; H, 5.25; N, 3.79.

The benzyl bromide salt of the dihydroisoquinoline, 127, was prepared from 2.77g (7.43mmole) of the free base and 1.85g (15mmole) of benzyl bromide according to the procedure described for the benzyl bromide salt 112 to give 4.08g (98%) of 127.

mp 143-145°C

ir (free base, KBr) cm⁻¹: 1660 (C=O).

nmr (salt, CD₃OD)(ppm):
3.15-3.80 (m, 4H, ArCH₂CH₂
overlapped with solvent peaks)
3.90 (s, 6H, 2xArOCH₃)
3.94 (s, 3H, 1xArOCH₃)
5.12 (s, 2H, ArCH₂N)
6.19 (s, 2H, OCH₂O)
6.88 (s, 1H, 1xArH)
7.11 (s, 1H, 1xArH)
7.27 (s, 2H, 2xArH)
7.44 (s, 5H, 5xArH)

Analysis for C\textsubscript{27}H\textsubscript{25}N\textsubscript{1}O\textsubscript{6}.1/2H\textsubscript{2}O:

Calculated: C, 59.02; H, 4.95; N, 2.55;

Found: C, 58.95; H, 5.30; N, 2.44.

1- and 2-(3',4',5'-trimethoxybenzoyl)-4,5-dihydro-7,8-methyleneoxy-3-benzyl-3H-3-benzazepine (128),(129)

![Chemical Structures](image)

The synthetic procedure for the two isomeric dihydrobenzazepines 128 and 129 is the same as the synthetic procedure for 113 and 114 using 0.64g (1.18mmole) of the benzyl bromide salt 127 in methanol and approximately 0.6g (15mmole) of diazomethane (generated from 4.25g of Diazald) in ether solution and after purification by column chromatography on silica gel by using 10% ether in chloroform (with 1% NH\textsubscript{4}OH) as eluent afforded 0.24g (43%) of the 1-benzoyl isomer 128 and 0.16g (28%) of the 2-benzoyl isomer 129 were isolated.

For the 1-benzoyl isomer 128:

mp 55-58°C

ir (free base, neat) cm\textsuperscript{-1}: 1645 (C=O), 1580 (aromatic)
nmr (free base, CDCl₃) (ppm):
  2.83-3.07 and 3.37-3.60 (each m, each 2H, ArCH₂CH₂N)
  3.77 (s, 6H, 2xArOCH₃)
  3.87 (s, 3H, 1xArOCH₃)
  4.36 (s, 2H, ArCH₂N)
  5.86 (s, 2H, OCH₂O)
  6.49 (s, 1H, =C-H)
  6.76 (s, 2H, 2xArH)
  6.84 (s, 1H, 1xArH)
  7.10-7.40 (m, 5H, 5xArH)
  7.43 (s, 1H, 1xArH)

Analysis for C₂₈H₂₇N₁O₆·3/2H₂O:
  Calculated: C, 67.19; H, 6.04; N, 2.80;
  Found: C, 67.54; H, 5.75; N, 2.70.

For the 2-benzoyl isomer 129:

mp 87-89°C

IR (free base, neat) cm⁻¹: 1655 (C=O), 1590 (aromatic)

nmr (free base, CDCl₃) (ppm):
  2.77-2.97 and 3.10-3.30 (each m, each 2H, ArCH₂CH₂N)
  3.87 (s, 6H, 2xArOCH₃)
  3.94 (s, 3H, 1xArOCH₃)
  4.04 (s, 2H, ArCH₂N)
  5.91 (s, 2H, OCH₂O)
  5.93 (s, 1H, =C-H)
  6.61 (s, 1H, 1xArH)
  6.68 (s, 1H, 1xArH)
7.23 (s, 2H, 2xArH)
7.26 (s, 5H, 5xArH)

Analysis for C_{28}H_{27}N_{1}O_{6}·7/4H_{2}O
Calculated: C, 66.58; H, 6.09; N, 2.77;
Found: C, 66.78; H, 5.70; N, 2.73.

1-(3',4',5'-Trimethoxybenzoyl)-7,8-methylenedioxy-3-benzyl-
2,3,4,5-tetrahydro-1H-3-benzazepine (130)

The synthetic procedure for the 1-benzoyle tetrahydrobenz-
azepine 130 is the same as described for 118 using 350mg
(0.74mmole) of the 1-benzoyle hydrobenzazepine 128 and
15ml of 1M diborane in THF solution to give 320mg (91%) of
130 as an oil from which the HCl salt was prepared and re-
crystallized from ethanol-ether.

mp 194-195 °C
ir (free base, neat) cm⁻¹: 1675 (C=O)
nmr (free base, CDCl₃) (ppm):
2.35-3.35 (m, 6H, ArCH₂CH₂N and ArCHCH₂N)
3.42 (d, 1H, 1/2xArCH₂N, J=13 Hz)
3.64 (d, 1H, 1/2xArCH₂N, J=13 Hz)
3.80 (s, 6H, 2xArOCH₃)
3.89 (s, 3H, 1xArOCH₃)
4.76 (m, 1H, ArCHCO)
5.86 (s, 2H, OCH₂O)
6.36 (s, 1H, 1xArH)
6.65 (s, 1H, 1xArH)
7.09 (s, 2H, 2xArH)
7.18 (s, 5H, 5xArH)

m/e (EI): 475(9.9%), 278(40.3%)

Analysis for C₂₆H₂₉N₁O₆.HCl.1/4H₂O:
Calculated: C, 65.11; H, 5.95; N, 2.71;
Found: C, 65.26; H, 6.13; N, 2.62.

1-(α-Hydroxy-3',4',5'-trimethoxybenzyl) - 7,8-methylenedioxy 3-benzyl-2,3,4,5-tetrahydro-1 H-3-benzazepine (131)

![Chemical Structure](image)

The synthetic procedure for the 1-(α-hydroxybenzyl) tetrahydrobenzazepine 131 is the same as described for 119 using 125mg (0.244mmole) of the 1-benzoyl tetrahydrobenzazepine 128 and 95mg (2.44mmole) of sodium borohydride to afford 126mg (99.7%) of 131 as HCl salt.

mp 198-201°C
ir (free base, neat) cm⁻¹: 3400 (OH), 1595 (aromatic)
nmr (free base, CDCl₃) (ppm):
  2.05-3.55 (m, 5H, ArCH₂CH₂N and ArCHCH₂N)
  3.62 (s, 2H, ArCH₂N)
  3.69 (s, 6H, 2xArOCH₃)
  3.77 (d, 2H, ArCHCH₂N, J=5.7Hz)
  3.78 (s, 3H, 1xArOCH₃)
  5.20 (d, 1H, ArCHOH, J=4.7Hz)
  5.76 (d, 1H, 1/2xOCH₂O, J=1.3Hz)
  5.79 (d, 1H, 1/2xOCH₂O, J=1.3Hz)
  6.03 (s, 1H, 1xArH)
  6.41 (s, 2H, 2xArH)
  6.56 (s, 1H, 1xArH)
  7.35 (s, 5H, 5xArH)
m/e (EI): 477(0.7%), 459(15.3%), 278(32%)

Analysis for C₂₈H₃₁N₁O₆·HCl·5/4H₂O:
  Calculated: C, 62.68; H, 6.48; N, 2.61;
  Found: C, 62.69; H, 6.52; N, 2.57.

1-(3',4',5'-trimethoxybenzylidenyl)-7,8-methylenedioxy
3-benzyl 2,3,4,5-tetrahydro-1H-3-benzazepine (132)
The synthetic procedure for the 1-benzylidenyl tetrahydrobenzazepine 132 is the same as the synthetic procedure for 120 using 216mg (0.42mmole) of the 1-α-hydroxybenzyl tetrahydrobenzazepine 131 and 160mg (0.84mmole) of the p-toluene sulfonic acid to give 198mg (95%) of 132 as HCl salt.

mp 172-175°C

ir (free base, neat) cm⁻¹: 1590 (aromatic)

nmr (free base, CDCl₃) (ppm):

2.87 (s, 4H, ArCH₂CH₂N)
3.32 (s, 2H, ArCCH₂N)
3.60 (s, 6H, 2xArOCH₃)
3.80 (s, 5H, 1xArOCH₃ and ArCH₂N)
5.83 (s, 2H, OCH₂O)
6.25 (s, 2H, 2xArH)
6.37 (s, 1H, =CH⁻)
6.46 (s, 1H, 1xArH)
6.68 (s, 1H, 1xArH)
7.33 (s, 5H, 5xArH)

m/e (EI): 459 (100%)

Analysis for C₂₈H₂₉N₁O₅·HCl

Calculated: C, 67.80; H, 6.10; N, 2.82;

Found: C, 67.61; H, 6.20; N, 2.74.
1-(3',4',5'-trimethoxybenzyl) - 7,8-methylenedioxy - 2,3,4,5-
tetrahydro-1H-3-benzazepine (133)

To a 50ml absolute ethanol solution of 81mg (0.16mmole) of
the 1-(benzylidenedyl) tetrahydrobenzazepine 132 was added
40mg of 10% Pd/C and the mixture was hydrogenated at 40
psi for 5.5 hr. The catalyst was then filtered through celite
and the filtrate thus obtained was evaporated in vacuo. The
residue was purified by column chromatography on silica gel
by using 5% methanol in chloroform (with 1% NH₄OH) as eluent.
From the residue the HCl salt was prepared and crys-
tallized from ethanol-ether to give 34.4mg (52%) of 133.

mp 175-177°C

ir (free base, neat) cm⁻¹: 3340 (NH), 1590 (aromatic)

nmr (free base, CDCl₃) (ppm):

2.60-3.35 (m, 10H, ArCH₂CH₂NH
and ArCH₂CHCH₂N)

3.81 (s, 6H, 2xArOCH₃)

3.82 (s, 3H, 1xArOCH₃)

5.89 (s, 2H, OCH₂O)

6.35 (s, 2H, 2xArH)
6.52 (s, 1H, 1xArH)  
6.62 (s, 1H, 1xArH)  
m/e (EI): 371 (13.2%), 90 (100%)  
Analysis for C\textsubscript{21}H\textsubscript{25}N\textsubscript{5}O\textsubscript{5}·HCl·1/2H\textsubscript{2}O:  
Calculated: C, 60.50; H, 6.53; N, 3.36;  
Found: C, 60.44; H, 6.83; N, 3.22.  

2-(3', 4', 5'-trimethoxybenzoyl)-7, 8-methylenedioxy-3-benzyl-2, 3, 4, 5-tetrahydro-1H-3-benzazepine (134)  

![](image)

The synthetic procedure for the 2-benzoyl tetrahydro benzazepine 134 is the same as described for 118 using 720mg (1.50mmol) of the 2-benzoyl dihydrobenzazepine 129 and 30ml of 1M diborane in THF solution to give 307mg (40%) of 134 as HCl salt.  
mp 215-218°C  
ir (free base, neat)cm\textsuperscript{-1}: 1680 (C=O)  
nmr (free base, CDCl\textsubscript{3}) (ppm):  
2.50-3.65 (m, 6H, ArCH\textsubscript{2}CH\textsubscript{2}N and ArCH\textsubscript{2}CHCO)  
3.86 (s, 6H, 2xArOCH\textsubscript{3})  
3.94 (s, 3H, 1xArOCH\textsubscript{3})  
3.77-4.07 (q, 2H, ArCH\textsubscript{2}N)
3.28-3.35 (q, 1H, ArCH₂CHO, J=7.9Hz).
5.89 (s, 2H, 2xArH)
6.41 (s, 1H, 1xArH)
6.61 (s, 1H, 1xArH)
7.24 (s, 5H, 5xArH)

m/e(EI): 280(100%), 475(1.9%)

Analysis for C₂₈H₂₉N₂O₆.HCl:

Calculated: C, 65.68; H, 5.91; N, 2.74;

Found: C, 65.54; H, 6.09; N, 2.54.

2-(α-Hydroxy-3',4',5'-trimethoxybenzyl)—7,8-methylenedioxy
3-benzyl-2,3,4,5-tetrahydro-1H-3-benzazepine (135)

The synthetic procedure for 2-(α-hydroxybenzyl) tetrahydrobenzazepine 135 is the same as described for 119 using 150mg (0.293mmole) of the 2-benzoyl tetrahydrobenzazepine 134 and 111mg (2.93mmole) of sodium borohydride to give 120mg (80%) of 135 as HCl salt.

mp 164-167°C
ir (free base, neat)cm⁻¹: 3340 (OH), 1600 (aromatic)
nmr (free base, CDCl₃) (ppm):
1.95-2.50 and 2.24-3.07
  (m, 7H, ArCH₂CH₂N and ArCH₂CHN)
3.79 (s, 6H, 2xArOCH₃)
3.83 (S, 3H, 1xArOCH₃)
3.85-4.35 (m, 3H, ArCH₂N and ArCHOH)
5.88 (d, 1H, 1/2xOCH₂O, J=1.3Hz)
5.92 (d, 1H, 1/2xOCH₂O, J=1.3Hz)
6.35 (s, 1H, 1xArH)
6.37 (s, 2H, 2xArH)
6.60 (s, 1H, 1xArH)
7.38 (s, 5H, 5xArH)

m/e (EI): 459(100%). (CI, isobutane): 478(1.4%, M+1)

Analysis for C₄₀H₂₆N₁O₆.HCl.9/8H₂O
  Calculated: C, 62.95; H, 6.46; N, 2.62;
  Found: C, 63.29; H, 6.86; N, 2.49.

2-(3',4',5'trimethoxybenzyl) — 7,8-methylenedioxy — 3-benzyl-2,3,4,5-tetrahydro-1H-3-benzazepine (136)
The synthetic procedure for the 2-benzyl tetrahydrobenzazepine 136 is the same as described for 123 using 180mg (0.35mmole) of 135, 2ml (0.79mmole) of thionyl chloride and 675mg (17.3mmole) of lithium aluminum hydride to afford 100mg (57%) of 136 as HCl salt.

mp 144-146°C

ir (free base, neat) cm⁻¹: 1590 (aromatic)

nmr (free base, CDCl₃) (ppm):

2.13-3.55 (m, 9H, ArCH₂CH₂N and ArCH₂CHCH₂Ar)

3.76 (s, 6H, 2xArOCH₃)

3.82 (s, 3H, 1xArOCH₃)

3.90 (s, 2H, ArCH₂N)

5.88 (d, 1H, 1/2xOCH₂O, J=1.6Hz)

5.93 (d, 1H, 1/2xOCH₂O, J=1.6Hz)

6.17 (s, 2H, 2xArH)

6.46 (s, 1H, 1xArH)

6.63 (s, 1H, 1xArH)

7.30 (s, 5H, 5xArH)

m/e (EI): 461 (0.9%), 280 (100%)

Analysis for C₂₈H₃₂N₂O₅·HCl·3/4H₂O:

Calculated: C, 65.75; H, 6.60; N, 2.74;

Found: C, 65.64; H, 6.78; N, 2.69.
\[2-(3',4',5'-\text{Trimethoxybenzyl})-7,8-\text{methylenedioxy}-2,3,4,5-\text{tetrahydro}-1\text{H}-3\text{-benzazepine} \text{ (137)}\]

To a 50ml absolute ethanol solution of 100mg (0.2mmole) of the 2- benzyl tetrahydrobenzazepine 136 was added 50mg of 10% Pd/C and the mixture was hydrogenated at 40 psi for 8hr. The catalyst was then removed by filtration though celite and the filtrate was evaporated in vacuo. The residue thus formed was purified by column chromatography on silica gel using 5% methanol in chloroform (with 1% \(\text{NH}_4\text{OH}\)) as eluent. From the residue the HCl salt was prepared and re-crystallized from ethanol-ether to give 72mg (88.3%) of 137 as HCl salt.

mp 211-213°C

ir (free base, neat) cm\(^{-1}\): 3320(NH), 1590 (aromatic)

nmr (free base, CDCl\(_3\)) (ppm):

\[\begin{align*}
2.45-3.35 & \text{ (m, 10H, ArCH}_2\text{CH}_2\text{NH} \\
& \text{ and ArCH}_2\text{CHCH}_2\text{Ar}) \\
3.85 & \text{ (s, 9H, 3xArOCCH}_3\text{)} \\
3.90 & \text{ (s, 2H, ArCH}_2\text{NH}) \\
5.92 & \text{ (s, 2H, OCH}_2\text{O)}
\end{align*}\]
6.44 (s, 2H, 2xArH)  
6.61 (s, 2H, 2xArH)  
m/e (EI): 371(1.6%), 190(100%)  
Analysis for C21H25N1O5·HCl  
Calculated: C, 61.84; H, 6.42; N, 3.43;  
Found: C, 61.68; H, 6.43; N, 3.36.  

Mannich reaction with 2-(3',4',5'-trimethoxybenzyl)-7,8-  
methylenedioxy-2,3,4,5-tetrahydro-1H-3-benzazepine(137)  

To a 1 ml ethanol solution of 20 mg (0.05mmole) of the  
2-(3',4',5'-trimethoxybenzyl)-7,8-methylenedioxy-2,3,4,5  
tetrahydrobenzazepine (137) was added 5 drops of 37% formaldehyde solution. The mixture was allowed to heat at reflux overnight. After allowing to come to room temperature, the mixture was extracted with chloroform and the chloroform layer was dried (MgSO4) and the solvent was removed in vacuo. The residue thus formed was purified by column chromatography on silica gel using 10% methanol in chloroform (With 1% NH4OH) as eluent. From the residue the HCl salt was prepared which was crystallized from ethanol-ether to give 15 mg (71%) of the product 138.
mp 218-219°C

ir (free base, neat) cm⁻¹: 1605 (aromatic)

nmr (free base, CDCl₃) (ppm):
1.85-2.15 and 2.50-4.15 (each m, 2H and 9H, ArCH₂CH₂NH, ArCH₂N and ArCH₂CH₂CHCH₂Ar)
3.80 (s, 3H, 1xArOCH₃)
3.81 (s, 3H, 1xArOCH₃)
3.85 (s, 3H, 1xArOCH₃)
5.90 (s, 2H, OCH₂O)
6.36 (s, 1H, 1xArH)
6.61 (s, 1H, 1xArH)
6.64 (s, 2H, 2xArH)

Analysis for C₂₂H₂₅N₁O₅HCl

Calculated: C, 62.93; H, 6.24; N, 3.34;
Found: C, 62.75; H, 6.21; N, 3.27.

Boron trichloride reaction with 1-(3',4',5'-trimethoxybenzyl) 7,8-methylenedioxy — 2,3,4,5-tetrahydro — 1H-3-benzazepine (133)

To a 5ml methylene chloride solution of 25mg (0.06mmole) of 133 was added 0.3ml (0.3mmole) of 1M methylene chloride solution of boron trichloride at 0°C under argon atmosphere. The mixture was then allowed to stir for 5hr and 0.2ml of absolute methanol was added to quench the reaction. After stir-
ring for another hour the mixture was evaporated in vacuo and the residue was crystallized from ethanol-ether to give 6mg (25%) of the catechol 65. The NMR spectrum matched with that of catechol 65 from catalytic hydrogenation. Thin layer chromatography on silica gel using ethylacetate:acetic acid:water=6:3:1 as eluent also indicated a matched spot with catechol 65 with a Rf value of 0.26.

**Boron trichloride reaction with 2-(3',4',5'-trimethoxybenzyl) 7,8— methylenedioxy—2,3,4,5-tetrahydro—1H-3-benzazepine (137)**

The synthetic procedure for the boron trichloride reaction of 2-(3',4',5'-trimethoxybenzyl)-7,8-methylenedioxy-2,3,4,5 tetrahydrobenzazepine (137) is the same as described above. Using 25mg (0.06mmole) of 137 and 0.3ml (0.3mmol) of 1M methylene chloride solution of boron trichloride afforded 10mg (41%) of the catechol 66. The NMR spectrum matched with that of catechol 66 from catalytic hydrogenation. Thin layer chromatography on silica gel using ethylacetate:acetic acid:water=6:3:1 as eluent also indicated a matched spot with catechol 66 with a Rf value of 0.33.
12-Chloro-5,6,7,7a-tetrahydro-2,3-dibenzylxyloxy-8,9,10-trimethoxy-7-methylindeno-[2,1a]-3-benzazepine (125)

To a 20ml benzene solution of 100mg (0.16mmole) of 1-benzoyl dihydrobenzazepine 113 was added 200mg (1.3mmole) of phosphoryl chloride (1.3mmole) and the mixture was allowed to heat at reflux for 30 min. After allowing to come to room temperature, the mixture was washed with 10% ammonia water and dried (MgSO₄) and the solvent was removed in vacuo, the residue thus formed was purified by column chromatography on silica gel using 2% ether in chloroform (with 1% NH₄OH) as eluent to give 75mg (71%) of the cyclized product 125.

mp 110-112°C

ir (free base, neat) cm⁻¹: 1605 (aromatic)
nmr (free base, CDCl₃) (ppm):

2.05-3.75 (m, 6H, ArCH₂CH₂NCH₂Ar)
3.82 (s, 3H, 1xArOCH₃)
3.92 (s, 3H, 1xArOCH₃)
4.21 (s, 3H, 1xArOCH₃)
4.98 (s, 1H, ArCHN)
5.17 (s, 4H, 2xArCH₂O)
6.69 (s, 1H, 1xArH)
6.74 (s, 1H, 1xArH)
7.10-7.60 (m, 16H, 16xArH)

Analysis for C₄₁H₃₈N₄O₅Cl.H₂O

Calculated: C, 72.61; H, 5.94; N, 2.06;

Found: C, 72.81; H, 5.68; N, 1.89.
BIOLOGICAL METHODS

The biological evaluations on the beta adrenergic systems were determined by Dr. Asoke Mukhopadhyay, the biological activities on human platelets were determined by Drs. Huzoor-Akbar, and Steven S. Navran.

Beta Adrenergic Activities

Guinea pigs of each sex (weighing 300-500g) were employed in all experiments. The isolation and procedures for testing of each compound in isolated guinea pig atria, trachea and auricle were identical with those described previously\textsuperscript{145,146}. Responses were recorded on a Grass (model 7) polygraph via FT-03 force displacement transducers. Cumulative dose-response curves were obtained according to the method of Van Rossum \textsuperscript{147}. 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. Maximal drug effects in a given tissue were compared with the maximal effect by isoproterenol added at the end of each experiment and expressed as a ratio value. Responses for agonists are expressed as pD\textsubscript{2} values (negative logED\textsubscript{50}). The antagonistic activities are expressed as pK\textsubscript{B} values (negative logK\textsubscript{B}) as described by Furchgott\textsuperscript{153}.
\[ K_B = \frac{\text{apparent equilibrium dissociation constant of the antagonist}}{[\text{Antagonist}] / \text{Concentration ratio}-1} \]

Concentration ratio = \[ \frac{ED_{50}(\text{Agonist alone})}{ED_{50}(\text{Agnoist + Antagonist})} \]

**Platelet Antiaggregatory Activities**

Blood was collected by venous puncture from normal human volunteers who reported to be free of medication for at least 10 days prior to blood drawing. Platelet-rich plasma was prepared as previously described\(^{62,104}\). Platelet aggregation studies were performed according to the turbidometric method of Born\(^{148}\) as modified by Mustard\(^{149}\) using a Payton model 600 aggregometer (Buffalo, N.Y.). The prostaglandin endoperoxide analog U-46619\(^{150}\) was used as a prototype agonist for the prostaglandin pathway. The secretion of platelet contents from the dense granules was measured by monitoring the release of radioactivity from platelets pre-labeled with \[^{14}\text{C}\text{-serotonin}\ (0.2 \mu\text{Ci}/3 \times 10^8 \text{platelets})\]. Secretion data were calculated as the percent of total radioactivity in platelets\(^{151}\). The phosphatidylinositol response was measured by monitoring the incorporation of radioactivity of platelet pre-incubated with \[^{14}\text{C}\text{-arachidonic acid}\ (0.5 \mu\text{Ci/ml})\] or \[^{32}\text{P}\text{-sodium phosphate}\ (0.1 \text{mCi/ml})\] according to the procedure described by Navran\(^{152}\).
SUMMARY

Trimetoquinol, 1-(3',4',5'-trimethoxybenzyl) - 6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline, is a potent beta adrenergic stimulant and also a platelet antiaggregatory agent. In order to study the structure-activity relationships of trimetoquinol on both the beta adrenergic receptors and on platelets, we have synthesized nine of the structural analogs of trimetoquinol and have evaluated the biological activities. The results showed that:

1. Substitutions more bulkier than mono methyl groups at alpha-benzylc position of trimetoquinol did not increase beta-2 activity but provided specificity. The erythro- and threo- isopropyl trimetoquinol analogs (59) and (60) even showed slight antagonistic activity toward beta-1 receptors.

2. The 1-naphthyl analogs (61) and (62) or the side chain extended analog (63) of trimetoquinol showed only marginal activities toward beta-1 and beta-2 receptors. However, compound 61 was an effective antagonist toward beta-1 receptors.

3. Ring expansion of tetrahydroisoquinoline to a tetrahydrobenzazepine ring system provided analogs 64, 65 and 66.
These three compounds showed lowered activities toward beta receptors. Compound 65 even became an antagonist.

4. The 2-tetrahydrobenzazepine analog of trimetoquinol 64 and its methylenedioxy analog 97 specifically blocked the phospholipase C induced platelet aggregation. These two compounds provided invaluable informations in the studies of the phospholipase C pathway.
REFERENCES


