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CERTAIN RIGID AND NON-RIGID ADRENERGIC AGENTS

DISSERTATION

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

by

Jon J. Fauley, B.S.

* * * * * * *

The Ohio State University
1971

Approved by

Adviser

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INTRODUCTION

In 1895 Oliver and Schaefer\(^1\) found that an extract of the adrenal gland produced a pressor effect. The active principle of this extract was isolated by Abel\(^2\) and named epinephrine by him. The chemical structure (1) was confirmed by the independent synthesis of epinephrine by Stolz\(^3\) and Dakin.\(^4\)

\[
\begin{align*}
\text{HO} & \quad \text{OH} \\
\text{HO} & \quad \text{CH-CH}_2\text{-NHCH}_3 \\
\end{align*}
\]

Elliot\(^5\) suggested that epinephrine was the neurotransmitter. As early as 1908 Cushny\(^6,7\) compared the pressor effects of the naturally occurring (−)-epinephrine with the synthetic (±)-epinephrine and discovered that (−)-epinephrine was two times as potent as (±)-epinephrine.\(^6\) He later compared (−)-epinephrine with (↑)-epinephrine and found that the latter was only one-twelfth to one-fifteenth as active as the former.\(^7\) These experiments demonstrated that optical isomers of epinephrine showed stereoselectivity in inducing pharmacologic effects. A large number of structural analogs of epinephrine were synthesized.
and studied with the dual aim of establishing new therapeutic agents and elucidating the mechanism of action of the adrenergic agents. The classical work of Barger and Dale, in which they studied the pharmacologic actions of a large series of synthetic amines related to epinephrine and in so doing determined the basic chemical requirements for adrenergic activity, exemplifies these studies. The research of Chen and co-workers on the alkaloid, ephedrine (2), led to the introduction of this compound into Western medicine as a bronchiodilator. Their work served as the impetus for chemical and pharmacologic research on noncatechol phenethylamines as potential adrenergic agents.

The early studies of the structure-activity-relationships among sympathomimetic agents culminated with the work of Ahlquist, who noted that two distinct orders of potency appeared in different tissues when testing epinephrine (1), norepinephrine (3), and isoproterenol (4). In some tissues the
order of potency was epinephrine ≥ norepinephrine >> isoproterenol, while in other tissues the order of potency was isoproterenol >> epinephrine ≥ norepinephrine. This observation led to the postulation that two types of adrenergic sites existed: the one, designated alpha and represented by those cases where the potency order was epinephrine ≥ norepinephrine >> isoproterenol, was associated primarily with excitation or contraction; the other, designated beta and represented by those cases where the potency order was isoproterenol >> epinephrine ≥ norepinephrine, was associated primarily with inhibition of function or relaxation. Further evidence for Ahlquist's alpha and beta classification comes from studies with adrenergic antagonists. Classic adrenergic blocking agents such as Dibenamine (5) or phentolamine (6) block most of the excitatory responses and, in general, do not block inhibitory responses. In
contrast, agents such as dichloroisoproterenol (7) and pronethalol (8) block
the inhibitory responses but do not affect the excitatory responses. The use

![Chemical Structures](image)

of blockers shows that many tissues have both \textit{alpha-} and \textit{beta-} receptors.

The discovery that cocaine potentiated the effects of epinephrine, but not
the effects of tyramine (9) and ephedrine (2), \textsuperscript{12} plus the observation that the
normal supersensitization of denervated structures to autonomic drugs is not
revealed with tyramine (9) \textsuperscript{13} led Burn \textsuperscript{14} to suggest that the effects of tyramine
(9) and ephedrine (2) were not mediated through a direct action at the adrenergic

![Chemical Structure](image)
receptor. Fleckenstein subsequently divided sympathomimetic amines into three classes: 1) those potentiated by denervation and cocaine (direct), 2) those unaffected by these procedures (mixed), and 3) those ineffective or significantly less effective afterward (indirect). The subsequent discoveries that reserpine depletes tissues of norepinephrine and that tyramine does not act on reserpenized tissue led Burn and Rand to conclude that some sympathomimetic amines act by releasing norepinephrine. The present concept of direct and indirect action thus evolved and has received ample experimental verification. In the simplest sense this concept suggests that sympathomimetic agents may act: 1) predominantly directly, that is, at the effector site, 2) predominantly indirectly, by releasing endogenous norepinephrine, or 3) by a combination of these processes. Structure-activity-relationships of the $\beta$-phenylethylamine moiety, which can be regarded as the parent nucleus of adrenergic amines, have been extensively studied. Maximum activity at both the alpha- and beta-receptor depends upon the phenolic hydroxyl groups in both the meta and para positions. When both of the phenolic groups are absent, the overall sympathomimetic activity is reduced and there is especially a reduction in beta-activity. However, it has been shown that direct activity is detectable in the noncatechol compounds like phenylpropanolamine, thus the phenolic hydroxyl groups present in very potent sympathomimetic agents cannot be assigned an indispensable structural requirement for adrenergic agonist activity. The necessity of the $\beta$-hydroxyl group for maximum activity has also been shown.
Numerous other modifications of the phenethylamine moiety have been made, such as α- and β-substitutions, but none of these modifications led to a significant increase in sympathomimetic activity.

In an effort to explain the stereoselectivity exhibited by the adrenergic receptor, Easson and Stedman advanced an hypothesis in 1938. They proposed that in an asymmetric molecule, like (-)-epinephrine, three of the four groups linked to the asymmetric carbon are concerned in the attachment with the receptor. These groups are: 1) the basic nitrogen, 2) the aromatic group (with the meta- and para-hydroxyl groups influencing the intensity of the attachment), and 3) the alcoholic hydroxyl group. Thus, to explain the difference in pressor activity of the enantiomeric epinephrine compounds, they suggested that the less active (+)-epinephrine because of its configuration has the β-hydroxyl group in the "wrong" position and thus reacts as though the hydroxyl group were missing from the molecule and only a two-point interaction is involved. To support the hypothesis it was shown that on guinea pig ileum (-)-epinephrine (1a) was more active than (+)-epinephrine (1b) which was equiactive with the deoxyderivative, epinine (10). Subsequent criticism of the
theory on the grounds that in many cases the activity of the deoxy derivatives
and the (d)-isomers was not similar caused the theory to be disregarded for
some time. In light of the concept of direct and indirect activity, Patil and
co-workers\textsuperscript{29,30} have tested the Easson-Stedman Hypothesis using a series
of (–)- and (d)-isomers and their deoxy derivatives. In normal vas deferens
preparations the (–)-isomer was always more active than the corresponding
d(–)-isomer, but many corresponding deoxy compounds were more active than
the (d)-isomer. However, in vas deferens preparations which had been pre-
treated with reserpin e to remove the indirect component of activity, the (–)-
isomer maintained its high activity while the (d)-isomer and the corresponding
deoxy derivative had a lower, but equal, activity. Thus, the Easson-Stedman
Hypothesis seems to hold only for sympathomimetic amines which exert their
effect via direct action on the adrenergic receptors.

Agreement with the Easson-Stedman Hypothesis has been demonstrated
also with noncatechol adrenergic agents. For example, (–)-phenethanolamine
(11a) produces inhibition of the rabbit ileum whereas (d)-phenethanolamine (11b)
and the deoxy derivative, phenethylamine (12), do not have intrinsic activity,
but both produce an equal antagonism of norepinephrine effects.\textsuperscript{31}

LaPidus and co-workers\textsuperscript{32} pointed out the stereochemical similarities between (−)-ephedrine (2a) and (−)-pseudoephedrine (2c). In both of these
molecules the functional groups, the phenyl ring, the \( \beta \)-hydroxyl group, and the amino group, could fit the same three points on a hypothetical receptor.

In the anesthetized cat the pressor and nictitating membrane effects of \((-\text{-})\)-ephedrine were promptly terminated by \((-\text{-})\)-pseudoephedrine. Pretreatment of an animal with \((-\text{-})\)-pseudoephedrine can also prevent the effects of \((-\text{-})\)-ephedrine. However, the observation that the antagonism by \((-\text{-})\)-pseudoephedrine can be extended to other indirectly acting amines suggests that the antagonism may be physiological.

A review of some pharmacologic studies employing the ephedrine isomers, \(1\text{R}, 2\text{S}-(\text{-})\)-ephedrine (2a), \(1\text{S}, 2\text{R}-(\text{+})\)-ephedrine (2b), \(1\text{R}, 2\text{R}-(\text{-})\)-pseudoephedrine (2c), and \(1\text{S}, 2\text{S}-(\text{+})\)-pseudoephedrine (2d), reveals the types of stereoselectivity exhibited by adrenergic receptors toward adrenergic agents. The
pattern of the indirect activity of the ephedrine isomers in the rat vas deferens appears as (-)-ephedrine > (+)-ephedrine ≥ (+)-pseudoephedrine >> (-)-pseudoephedrine. The pattern of the potentiation of exogenous norepinephrine by these compounds in reserpine-pretreated tissues also appears to be the same. On the isolated rabbit aorta (-)-ephedrine produces a marked contractile effect while other isomers produce little or no effect. On the anesthetized dog (-)-ephedrine was the best pressor isomer, (+)-ephedrine and (+)-pseudoephedrine had weaker pressor activity, while (-)-pseudoephedrine was a depressor agent.

Investigations of the effects of the ephedrine isomers on tracheal smooth muscle of guinea pig showed that all isomers appeared to be partial agonists, and (-)-ephedrine and (-)-pseudoephedrine were mainly direct acting, whereas the smooth muscle effects of (+)-ephedrine and (+)-pseudoephedrine were considerably reduced by reserpine-pretreatment. Pendular movements of the rabbit ileum are inhibited only by (-)-ephedrine; the other three isomers produce little or no effect and are antagonistic to the α-adrenergic inhibiting effects of (-)-norepinephrine in a nonstereo-specific manner.

Portoghese has conducted nuclear magnetic resonance spectroscopy studies to determine the solution conformation of ephedrine. He suggests that the ground state conformation of the protonated forms of (-)-ephedrine (13) and (-)-pseudoephedrine (14) differ only in the orientation of the C-methyl group, and it is possible that the methyl group in the case of (-)-pseudoephedrine hinders
effective interaction with adrenergic receptors. It is also pointed out by the

![Diagram](image)

author that the internal hydrogen bonding provides the possibility of stabilizing
the amines in a conformation favorable to the amine-receptor association and
could render the alcoholic proton more acidic and consequently promote stronger
hydrogen bonding with the receptor.

Since studies to determine the preferred solution conformation do not answer the question of the conformation assumed by an adrenergic agent at
the receptor site, numerous investigators have turned to the design of rigid
analogs of active adrenergic agents. Such compounds present a fixed conformation to the receptor. The cis-2-amino-4-methyl-5-phenyl-2-oxazoline (15) was
prepared and found to possess pharmacologic effects similar to ephedrine. 40
The cis- (16) and trans-2-aminotetralol (17), which are norephedrine (18) analogs, were also prepared; and it was found that the (4)-cis-2-aminotetralol, which corresponds to the most active form of norephedrine, was the most active pressor agent.

Smissman and co-workers have prepared a number of transdecalin analogs as rigid models of adrenergic agents. The d1-3-amino-2-phenyl-trans-2-decalols (19), (20), (21), and (22) were found to be nonstereoslective in their effects on vas deferens preparations. The d1-3-phenyl-3-hydroxy-trans-deca-
hydroquinolines (23) and (24) were found lacking alpha-response on the vas deferens, but they were observed to potentiate the response to norepinephrine.

The d1-3-amino-2-(3,4-dihydroxyphenyl)-trans-2-decalol hydrochlorides (25), (26), (27), and (28) were found to be stereoselective in their relative rates of
0-methylation by catechol-0-methyltransferase with compound 25 being 0-methylated most rapidly. The d1-3-amino-2-(3,4-dihydroxyphenyl)-trans-2-decalin hydrochlorides (29), (30), (31), and (32) were also found to be stereoselective in their relative rates of 0-methylation by catechol-0-methyl transferase with compound 30 being 0-methylated most rapidly.
The 9-hydroxy-10-amino-1, 2, 3, 4, 4a, 9, 10, 10a-(trans-4a, 10a)-octahydrophenanthrenes (33), (34), (35), and (36) were also prepared as rigid analogs of norephedrine. These compounds were found to have minimal, nonstereoselective effects as agonists on vas deferens preparations while compounds 33 and 35 were found to have adrenergic blocking activity.
Numerous workers have attempted to visualize the adrenergic receptor at the molecular level. Belleau first advanced such a visualization. He felt that the ability of the agonist amine group to effect ion-pair formation determines an alpha-response while larger substituents on the amine nitrogen, which prohibit ion pairing allow the beta-response to predominate through the facilitation of cyclic AMP formation. He suggested that the catechol moiety, acting through a metal chelation mechanism at the beta site, was instrumental in the latter response. The $\beta$-hydroxyl group was pictured as acting as some kind of pivot which increased affinity for either site. Belleau's "Conformational Perturbation Theory" visualized the drug molecule inducing a conformational change in the receptor, which he suggested was a protein-like molecule. The receptor could accommodate the drug molecule and lead to the given response.
proposal has met with much criticism. For example, the ion-pairing mechanism for \textit{alpha}-agonism leads to an anticipated structure-activity sequence for catecholamines of norepinephrine $>$ epinephrine $>$ isoproterenol since among amines of comparable basicity effective cationic head size is the only structural determinant of biological activity that is invoked. In fact, in a number of tissues epinephrine is a more effective \textit{alpha}-agonist than is norepinephrine. Also, Belleau's model invokes a vital role for the catechol moiety while, in fact, compounds lacking the catechol system have been shown to have significant agonist activity.

Bloom and Goldman in their "Dynamic Receptor Hypothesis" visualize the adrenergic receptor as being built around phosphorolytic enzymes which utilize adenosine triphosphate (ATP) as their specific substrate and function at a basal rate in the absence of exogenous stimulation. The role ascribed to catecholamine agonists at these receptors involve their ability to stimulate the rates of these phosphorolysis and phosphoryl group transfer reactions. This is accomplished by a direct interaction with the nucleotide substrate-phosphorolytic enzyme complex, in which the catecholamine functions as an activator.

The adrenergic receptors, therefore, are visualized as enzyme-substrate complexes. Since the production of a response by the interaction of such a system with a catecholamine agonist necessarily involves substrate destruction, in effect, it involves receptor destruction. The nature of the destructive process, however, allows rapid receptor regeneration as long as unbound nucleo-
tide substrate is available in the biophase; hence the name dynamic receptor.

It is implicit in this hypothesis that two different types of phosphorolytic enzymes underlie adrenergic processes. The alpha- and beta-responses are thought to be a direct result of that duality of enzymes. It is postulated that all alpha-responses emanate from an identical enzymic event as do all beta-responses. The observed differences in gross function that occur in various tissues as a result of a given type of adrenergic response are attributed to factors which predominate subsequent to the initial event.

The validity of this hypothesis has also been questioned. For example, the fact that the tertiary amine, N-methyl epinephrine, has alpha-agonist activity is inconsistent with the picture.

Although Belleau has revised his hypothesis somewhat and other suggestions have been made as to the molecular occurrences, it seems obvious that the mechanism of action of adrenergic agents at the molecular level is still unknown.

In addition to their effects on the physiological responsiveness of smooth muscle, catecholamines also have important actions on glycogenolytic and lipolytic metabolic pathways. It is known that epinephrine increases blood sugar levels. The effect is stereoselective in favor of (-)-epinephrine, and this effect is claimed to be due to activation of the beta-receptor. The sequence of events which is believed to be occurring in liver glycogenolysis involves catecholamines and adenyl cyclase stimulating the formation of cyclic AMP from
ATP. This cyclic AMP activates dephosphophosphorylase to the phosphorylated, active phosphorylase which in turn catalyses glycogen breakdown to glucose. Similarly, in the skeletal muscle catecholamines increase the activity of phosphorylase and initiate glycogenolysis through a series of reactions essentially similar to those occurring in the liver.

Numerous reports have suggested that the sympathetic nervous system and the catecholamines, norepinephrine and epinephrine, are involved in the mobilization of free-fatty acids from adipose tissue. For example, the injection of epinephrine or norepinephrine elevates plasma free-fatty acids, and the addition of these catecholamines to an incubation medium containing adipose tissue enhances the release of free-fatty acids. Other lines of evidence, particularly the location of adrenergic nerve elements near the fat cell and the presence of norepinephrine in the epididymal fat pad, have led to considerable interest in the underlying mechanism of adrenergic stimulation in fat tissue.

Several investigators have shown that catecholamine-induced lipolysis occurs along pathways similar to the glycogenolytic process of the liver. That is, the catecholamines initiate the release of free-fatty acids by interaction with adenyl cyclase which catalyzes the formation of cyclic AMP from ATP. The cyclic nucleotide is believed responsible for the conversion of an inactive lipase to an active lipase which in turn catalyzes the stepwise hydrolysis of trigly-
cerides to yield free-fatty acid and glycerol. This procedure is outlined in Scheme 1.

Several investigations have been conducted to quantitate differences between structural analogs of the phenethylamine molecule. The presence of either the catechol moiety or a monohydroxylated ring appeared necessary to confer optimal activity, while the presence of a 6-hydroxyl group or a large alkyl or aralkyl group on the amine nitrogen enhanced the fat mobilizing activity of the agonist molecule. In compounds lacking ring hydroxyls, for example, ephedrine and amphetamine, no agonist activity was observed. Although lipolysis is now believed to be \textit{beta}-receptor mediated, both \textit{alpha}- and \textit{beta}-adrenergic blocking agents have been shown to inhibit catecholamine induced lipolysis. However, \textit{beta}-blocking agents are considerably more
potent than alpha-blocking agents, and beta-blocking agents are competitive antagonists of epinephrine-induced lipolysis whereas alpha-blocking agents are non-competitive agents.

Sympathomimetic amines are known to possess central activity. Many of these amines show no central effect when administered peripherally due to their inability to cross the blood-brain barrier. However, certain of the noncatechol amines, for example amphetamine (37) and ephedrine, do cross the blood-brain barrier. Numerous tests with optically active adrenergic agents show that a stereoselectivity exists in the central nervous system. The (+)-amphetamine isomer was shown to be more effective than the (-)-isomer in producing central stimulation. Studies with the ephedrine isomers demonstrated that (-)-ephedrine, while not as effective as (+)-amphetamine, was a better central locomotor stimulant than the other ephedrine isomers. Other investigations involving the stereoisomers of ephedrine in numerous standard central testing procedures indicated that in a full profile of central activity the (-)- and (+)-ephedrines were much more potent than the (-)- and (+)-pseudo-
ephedrines. In studies involving the optical isomers of norepinephrine applied iontophoretically, it was shown that (−)-norepinephrine was more effective than (†)-norepinephrine in inducing excitatory responses, but that the two isomers were equally effective in inducing inhibitory responses.

The uptake of catecholamines and related phenethylamines via the noradrenergic neuronal membrane pump has been shown to be stereoselective in certain peripheral tissues. Similar stereoselectivity was recently demonstrated in the noradrenergic synaptosomes of the rat brain. The dopaminergic synaptosomes, however, failed to show stereoselectivity with either norepinephrine or amphetamine. Surprisingly, the 1R-enantiomer of pipradrol (38) possesses most of the central excitatory activity whereas the 1S-enantiomer of amphetamine possesses most of the central activity of that compound.

![Chemical Structure](image)

Diastereomeric methylphenidate has been shown to inhibit the uptake and binding of norepinephrine or its structural analogs in peripheral organs; for example, in the isolated rabbit aorta, in the isolated vas deferens, and in the reserpen-
ized rat iris. \textsuperscript{81} Investigations with the resolved methylphenidates revealed that both \textit{three} enantiomers were much more effective than the \textit{erythro} enantiomers in the isolated rabbit aorta. \textsuperscript{77} Stereoselectivity has also been demonstrated in the central nervous system for methylphenidate \textsuperscript{(39)}.\textsuperscript{82}

\begin{center}
\begin{tikzpicture}
\node (A) at (0.5,0) {COOMe};
\node (B) at (1,-0.5) {\ CH \hspace{0.5cm} \ N} ;
\end{tikzpicture}
\end{center}

\textsuperscript{39}

The discussion to this point reveals that despite numerous kinds of approaches and a staggering amount of work the architectural features of the adrenergic receptor site remain to be delineated. Due to the lack of appropriate techniques for directly examining the adrenergic receptor, information concerning the adrenergic receptor must be obtained by indirect methods. One of the most useful indirect methods involves altering the chemical character of agonist molecules and noting the resulting effect on a pharmacologic response. Due to the stereoselectivity of the adrenergic receptor site, the biological testing of optical isomers of adrenergic agents should reveal information concerning the stereochemical requirements of the adrenergic receptor. The adrenergic agent, ephedrine, has been extensively studied to elucidate stereochemical requirements of the adrenergic receptor\textsuperscript{(83)} since this molecule possesses two
asymmetric centers and thus four stereoisomers.

In an attempt to extend existing knowledge of the stereochemical requirements of the adrenergic receptor, the stereoisomers of an ephedrine analog, phenyl-2-piperidyl carbinol (40), were desired. This synthetic ephedrine anal-

![Chemical structure](image.png)

log has the freely rotating N-methyl and α-methyl moieties of ephedrine incorporated into a somewhat constrained piperidine ring. Due to the previously mentioned free rotation about single bonds in flexible molecules like ephedrine or phenyl-2-piperidyl carbinol, the solution conformation assumed by these compounds during interaction with the receptor cannot be assigned with certainty. Preferred ground state conformations, which have been assigned for ephedrine, cannot be extended to the solution state because a less stable conformation could be stabilized through receptor interactions and thus be the biologically active conformation.

Despite the limited activity possessed by the conformationally rigid analogs of adrenergic agents prepared to date, the concept of freezing the confor-
mation via the design of a rigid system remains as quite an attractive probe of
the adrenergic receptor. The low activity exhibited by some of the rigid ana-
logs, for example the trans-decalins and the octahydrophenanthrenes, has been
attributed to the addition of extraneous bulk which could sterically impede inter-
action or influence lipid solubility to the point of altering the availability of the
analog. Although a certain amount of bulk was added to the ephedrine molecule
in preparing the phenyl-2-piperidyl carbinol analog, a rigid analog of phenyl-2-
piperidyl carbinol could be prepared with no additional atoms being added. Thus,
if the four position of the piperidine ring in phenyl-2-piperidyl carbinol is bond-
ed to the ortho position of the benzene ring, 8-hydroxy-6,7-benzomorphan (41)
is generated. Despite the three asymmetric centers in 8-hydroxy-6,7-benzo-

\[
\begin{align*}
\text{OH} & \quad \text{H} \\
\text{CH} & \quad \text{N} \\
\text{phenyl} & \quad \text{piperidine ring} \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{H} \\
\text{N-H} & \quad \text{phenyl ring} \\
\end{align*}
\]

\[41\]

moran, only two diastereomers exist because of the bonding limitations im-
posed by this rigid system. Another objective of this investigation, therefore,
was the preparation of the diastereomeric 8α- and 8β-hydroxy-6,7-benzomor-
phans (41a and 41b respectively) as potential adrenergic agents. The former
diastereomer can be seen to coincide with the threo configuration; the latter
diastereomer, with the erythro configuration.

Since the stereoisomers of phenyl-2-piperidyl carbinol and the diastereomers of 8-hydroxy-6,7-benzomorphan were designed as potential adrenergic agents, it was desirable to biologically evaluate these compounds as peripheral adrenergic agents. Also, the chemical similarity between phenyl-2-piperidyl carbinol and the central stimulants, methylphenidate and pipradrol seemed to warrant the evaluation of the stereoisomers of phenyl-2-piperidyl carbinol as potential central adrenergic agents.
RESULTS AND DISCUSSION

Synthesis and Absolute Configuration of the Phenyl-2-Piperidyl Carbinols.

Phenyl-2-piperidyl carbinol was first reported in 1930 by Crook and McElvain, who described the reduction of phenyl-2-pyridyl ketone with hydrogen and Adam's catalyst (platinum oxide). The resultant diastereomeric phenyl-2-piperidyl carbinols were separated via fractional crystallization, but Crook and McElvain made no attempt to assign the configuration of the diastereomers labeling them only as compounds A and B. Swanson examined these diastereomers in a series of gross, nonquantitative pharmacologic tests and noted that the phenyl-2-piperidyl carbinols possessed several pharmacologic effects also possessed by ephedrine; for example, pressor activity and ability to shrink the nasal passages. It was not until 1961 that Dudas and Weisz, using an acyl migration study, determined that the compound A of Crook and McElvain possessed the erythro configuration; the compound B, the threo configuration.

In the hands of this author, reduction of phenyl-2-pyridyl ketone (42) with either hydrogen/platinum oxide or sodium/ethanol afforded only phenyl-2-pyridyl carbinol (43).
The inability to reproduce the work of Crook and McElvain could conceivably be due to the quality of the Adam's catalyst used. Frampton and co-workers performed a series of studies demonstrating the great variability of Adam's catalyst from batch to batch. Upon switching to hydrogen and Brown's catalyst, which is a finely divided platinum supported on charcoal and more active than Adam's catalyst, the reduction of phenyl-2-pyridyl ketone (42) to the diastereomeric phenyl-2-piperidyl carbinols (40a and 40b) proceeded smoothly in either a Brown Hydrogenator at atmospheric pressure and ambient temperature or a Parr Hydrogenator at forty pounds per square inch initial pressure and ambient temperature. The erythro (40a) and threo (40b) diastereomers
were separated via fractional crystallization using ethanol and ether as co-solvents. It has been demonstrated\(^{38,92}\) that for ephedrine and other related \(\beta\)-phenethylamines that the coupling constant between the benzylic proton, \(H_A\), and the vicinal proton, \(H_B\), was 2-4 Hz for compounds with the **erythro** configuration and 8-10 Hz for compounds with the **threo** configuration. Therefore, the observation that the coupling constant of the Dudas and Weisz assigned **erythro** diastereomer was \(J_{AB} = 3.3\) Hz (Figure 1) and of the Dudas and Weisz assigned **threo** diastereomer was \(J_{AB} = 9.3\) Hz (Figure 2) confirms the Dudas and Weisz assignment.

Resolution of the diastereomers of phenyl-2-piperidyl carbinol was next attempted with the initial procedures patterned after successful resolutions in the ephedrine series.\(^{93}\) After numerous attempts employing enantiomeric tartaric acid, mandelic acid, and di-p-toluoyl-tartaric acid as resolving agents and numerous solvent systems to effect fractional crystallization, it was found that **erythro**-phenyl-2-piperidyl carbinol (40a) could be resolved using mandelic
Figure 1. NMR of erythro-phenyl-2-piperidyl carbinol.
Figure 2. NMR of threo-phenyl-2-piperidyl carbinol.
acid as the resolving agent to yield the corresponding (-)- (40c) and (+)- (40d) enantiomers. Likewise, it was found that threo-phenyl-2-piperidyl carbinol (40b) could be resolved using di-p-toluoyl-tartaric acid as the resolving agent to yield the corresponding (-)- (40e) and (+)- (40f) enantiomers.
With the four stereoisomers of phenyl-2-piperidyl carbinol available, it was desirable to assign the absolute configuration to these isomers. The absolute configuration of the ephedrine isomers has been well established: \(^94\) (-)-ephedrine has the 1R, 2S configuration, \((\dagger)\)-ephedrine has the 1S, 2R configuration, (-)-pseudoephedrine has the 1R, 2R configuration, and \((\dagger)\)-pseudoephedrine has the 1S, 2S configuration. It has recently been reported that the \(^1\lambda_b \pi \rightarrow \pi^*\) transition, \(^95\) as measured by circular dichroism spectroscopy, serves as a reliable guide to the absolute configuration in both the ephedrine and the chloramphenicol series. \(^96\) The circular dichroism spectra was determined for each
of the stereoisomers of phenyl-2-piperidyl carbinol and the resultant Cotton curves (Figure 3) correlated quite nicely with the Cotton curves of the ephedrine isomers (Figure 4). Each of the eight stereoisomers can be seen to have three absorption maxima at 267 ± 1 μm, 261 ± 1 μm, and 255 ± 1 μm which are well defined, except for the 255 ± 1 μm absorption of (−)-pseudoephedrine. Also, the relative amplitude of the erythro and threo isomers coincide in each series with the erythro isomers absorbing with greater amplitude than the threo isomers. Thus, on the basis of the excellent correlation between the circular dichroism curves the absolute configuration is assigned to the stereoisomers of phenyl-2-piperidyl carbinol. The assignment is summarized in Table 1.

**TABLE 1

ABSOLUTE CONFIGURATION OF THE STEREOISOMERS
OF PHENYL-2-PIPERIDYL CARBINOL**

<table>
<thead>
<tr>
<th>Stereoisomer</th>
<th>Absolute Configuration (β:α)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(−)-erythro-phenyl-2-piperidyl carbinol (40c)</td>
<td>1R, 2S</td>
</tr>
<tr>
<td>(+)-erythro-phenyl-2-piperidyl carbinol (40d)</td>
<td>1S, 2R</td>
</tr>
<tr>
<td>(−)-threo-phenyl-2-piperidyl carbinol (40e)</td>
<td>1R, 2R</td>
</tr>
<tr>
<td>(+)-threo-phenyl-2-piperidyl carbinol (40f)</td>
<td>1S, 2S</td>
</tr>
</tbody>
</table>
Figure 3. The circular dichroism spectrum of the stereoisomers of phenyl-2-piperidyl carbinol.
Figure 4. The circular dichroism spectrum of the stereoisomers of ephedrine.
Synthesis of the Diastereomeric 8-Hydroxy-6,7-Benzomorphans

The 6,7-benzomorphan (44) ring system was initially prepared by May and Murphy during the systematic stripping of atoms from the morphine molecule which occurred during an extensive attempt to separate the desirable analgetic activity of morphine from its undesirable effects. Most of the work with the benzomorphan system has involved the synthesis of various 2,5,9-substituted derivatives as potential analgetics; an undertaking which culminated with the introduction of phenazocine (45) and pentazocine (46) onto the analgetic market.
Three somewhat general pathways into the benzomorphan system were developed during the analgetic studies; each of which was useful in the synthesis of certain derivatives. The first approach involved starting with hydrotroponitrile and is outlined in Scheme 2. 97

Scheme 2

\[ \text{CHO} \quad \begin{array}{c}
\phi-C-CH_2-CH_2-N-Me_2 \\
\text{CH}_3
\end{array} \quad \xrightarrow{1. \text{NC-CH}_2-\text{COOMe}/B;} \quad \xrightarrow{2. \text{H}_2/\text{PtO}_2} \quad \xrightarrow{3. \text{H}^+}, \Delta \quad \begin{array}{c}
\text{HO-C} \\
\text{NMe}_2 \\
\text{Me}
\end{array} \]

1. Br\(_2\)/HOAc
2. \(\Delta\)
3. dry distillation
The second approach\textsuperscript{99} involved an application of the Grewe morphinan synthesis\textsuperscript{100} and is outlined in Scheme 3.

Scheme 3

The third approach\textsuperscript{101} involved an application of the Baltrop synthesis\textsuperscript{102} and is outlined in Scheme 4.
However, attempts in the early 1960's to synthesize the parent 2-methyl-6,7-benzomorphan via the above methods failed, and it was not until 1968 that a synthesis of 2-methyl-6,7-benzomorphan from 4-phenylpyridine was reported. In 1969 a second synthesis from pyridine was reported.

This author believed that if the benzomorphan ring system, lacking alkyl substitution at either position five or nine, could be prepared then the appropriate
manipulations could be effected to prepare the diastereomeric 8-hydroxy-6,7-benzomorphans. Therefore, the initial approach into the benzomorphan system involved the synthesis of 2-methyl-8-oxo-6,7-benzomorphan (72)\textsuperscript{103,104} (Scheme 5). Thus, 4-phenylpyridine (64) was converted to the corresponding N-oxide (65) with hydrogen peroxide according to the method of Ochiai,\textsuperscript{105} and 1-methoxy-4-phenylpyridinium methyl sulfate (66) was subsequently formed upon treatment of the N-oxide with dimethyl sulfate. Nucleophilic displacement with sodium cyanide afforded 2-cyano-4-phenylpyridine (67) which was converted to 2-carbomethoxy-4-phenylpyridine (68) via methanolysis. N-methylation with methyl iodide gave the corresponding 1-methyl-2-carbomethoxy-4-phenylpyridinium iodide (69) which was catalytically reduced to 1-methyl-2-carbomethoxy-4-phenylpiperidine (70) with hydrogen/platinum oxide. Ester hydrolysis in refluxing hydrochloric acid yielded the 1-methyl-2-carboxy-4-phenylpyridine (71) which was cyclized to 2-methyl-8-oxo-6,7-benzomorphan (72) in hot polyphosphoric acid.
Scheme 5

64 \xrightarrow{H_2O_2} 65 \xrightarrow{Me_2SO_4} 66

67 \xrightarrow{NaCN} 68

69 \xrightarrow{MeI} 70 \xrightarrow{H_2/PtO_2}
With the exception of the polyphosphoric acid cyclization which proceeded in only an 11 percent yield, the yields of the reactions in this synthesis were acceptable. However, the rather large number of reactions coupled with the low yield in the cyclization led to an overall yield of only 1.7 percent.

Attention was next shifted to the synthesis of 2-methyl-6,7-benzomorphan as a possible starting material (Scheme 6). Thus, pyridine (73) was N-methylated with methyl iodide giving 1-methylpyridinium iodide (74) which was reduced to 1-methyl-1,2,5,6-tetrahydropyridine (75) with sodium borohydride in aqueous 1 normal sodium hydroxide. Benzylolation afforded the 1-benzyl-1-methyl-1,2,5,6-tetrahydropyridinium chloride (76) which was converted, via a Stevens rearrangement using phenyl lithium as the base, to the 1-methyl-2-benzyl-1,2,5,6-tetrahydropyridine (77). Treatment with hot polyphosphoric acid effected cyclization to the 2-methyl-6,7-benzomorphan (78).
The yields of the last two steps in this sequence were only 12.5 percent and 17.1 percent respectively, which lowered the yield of an otherwise highly acceptable synthetic scheme to only 1.2 percent. Despite the low yield this scheme involved only five steps which could all be easily scaled up to enable the
production of a reasonably large quantity of 2-methyl-6,7-benzomorphan as starting material. If 2-methyl-6,7-benzomorphan were to be used as starting material, it would be necessary to make two modifications in order to obtain the desired 8-hydroxy-6,7-benzomorphan; namely an oxygen function had to be introduced at position eight, and the methyl group had to be removed from position two.

The initial attempts at N-demethylation using the von Braun cyanogen bromide reaction or diethylazodicarboxylate provided a way to obtain 6,7-benzomorphan (79), but the yields were only 9 percent and 38.2 percent respectively and the route was abandoned. Oxidation of 2-methyl-6,7-benzomorphan (78), on the other hand, afforded the 2-methyl-8-oxo-6,7-benzomorphan (72) in 72 percent yield and proved to be a usable reaction in the synthesis.

Thiele's reagent, which consists of chromium trioxide, acetic anhydride, and sulfuric acid, was used as the oxidizing system. The postulated acylal interme-
diate (80) if formed was hydrolysed to the 8-oxo-derivative (72) during the basic workup of the reaction mixture.

\[ \text{CH}_3\text{C}_\text{r}_\text{O}_3\text{Ac}_2\text{O}\text{N-Me} \]

The possibility of obtaining both 2-methyl-8α-hydroxy- (81a) and 2-methyl-8β-hydroxy-6,7-benzomorph (81b) via the reduction of 2-methyl-8-oxo-6,7-benzomorph (72) seemed conceivable from a theoretical point of view. If one examined the three-dimensional representation of 2-methyl-8-oxo-6,7-benzomorph (72), it appeared obvious that the top side of the molecule was much more sterically hindered than the bottom side of the molecule. Therefore, cata-
lytic hydrogenation, which involves the least hindered side of a molecule approaching the catalyst surface for hydrogen transfer, would be expected to lead to the β-hydroxy epimer. Since there is a possibility of internal delivery by the basic nitrogen, metal hydride reduction could conceivably lead to either the α-hydroxy epimer, if internal delivery occurs, or the β-hydroxy epimer, if steric effects predominate in the absence of internal delivery. Dissolving metal reductions usually lead to the most energetically stable compound; thus it was conceived that the α-hydroxy epimer could be formed if steric effects predominate. However, the possibility of hydrogen bonding would favor the β-hydroxy epimer. To test the theoretical proposals 2-methyl-8-oxo-6,7-benzomorphan (72) was reduced with hydrogen/platinum oxide, sodium borohydride, lithium aluminum hydride, and sodium/propanol. The first three reductions
yielded only 2-methyl-8β-hydroxy-6,7-benzomorphan (81b), while the dissolv-

ing metal reduction led to no identifiable product. The structure assigned to
81b was consistent with the NMR and IR spectra, and the relative configuration
was assigned on the basis of the coupling constant, J_{HAHC}, being 6.5 Hz (see
discussion below and Table 2).

Nuclear magnetic resonance spectroscopy proved to be a useful tool in
assigning the relative configuration of the benzylic substituents. In the analysis
of NMR spectra, one of the commonly encountered proton-proton interactions is
the vicinal coupling. By taking advantage of the vicinal coupling constants of the
benzylic protons (H_A and H_B), which by nature of their relationship with the ar-
omatic ring and the hydroxyl group have chemical shifts in an uncluttered portion
of the NMR spectrum, the relative configuration of several of the synthesized
compounds could be assigned. Karplus^{114} first predicted that there was a rela-
tionship between the dihedral angle (φ) and the vicinal coupling constant such that
the coupling constant was at a maximal value at $\phi = 0^\circ$ and $180^\circ$ and at a minimal value at $\phi = 90^\circ$. A number of other factors have subsequently been shown to influence the coupling constant between vicinal protons. Coupling constants generally decrease 1) with an increase in the electronegativity of the substituents, 2) with an increasing number of electronegative substituents, 3) with an increase in the carbon-carbon bond length, and 4) with an increase in the angle between the protons and the carbon-carbon bond.

The values generally observed for coupling constants of protons on adjacent carbons in cyclic six-membered rings are: 1) vicinal diaxial, $J_{aa} = 8$-14 Hz and 2) vicinal axial-equatorial and diequatorial, $J_{ae} = J_{ee} = 1$-7 Hz. When one considers the 6,7-benzomorphan (44) system, the B ring can be looked upon as possessing a half-chair conformation with the two groups attached to
carbon eight occupying pseudo-axial and pseudo-equatorial positions. Protons occupying these positions will be designated $H_A$ and $H_B$ respectively. The vicinal proton of interest, which will be designated $H_C$, is located in the equatorial position of the B ring. Thus, the coupling constants $J_{HAHC}$ and $J_{HBHC}$ in an 8-substituted-6,7-benzomorphan system would be expected to be between 1-7 Hz. In a system resembling the 6,7-benzomorphan system, namely 9,10-disubstituted-1,2,3,4,4a,9,10,10a-(trans-4a,10a)-octahydrophenanthrene (82), it was shown that $J_{HXHZ}$ was usually 4.5-5 Hz while $J_{HYHZ}$ was 2-3.3 Hz, where $H_X$ is a pseudo-axial proton, $H_Y$ is a pseudo-equatorial proton, and $H_Z$ is an equatorial proton. Also, the former chemical shift was further down-
field than the latter by a partial \( \Delta \) unit. Thus, in the benzomorphan system it would analogously be expected that \( J_{HAHC} \) would be greater than \( J_{HBHC} \) and that the absorption of \( H_A \) would appear further downfield than the absorption of \( H_B \). If one examines molecular models of the benzomorphan system, \( J_{HAHC} \) would theoretically be expected to be larger than \( J_{HBHC} \) since the dihedral angle between \( H_A \) and \( H_C \) is about 30° while the dihedral angle between \( H_B \) and \( H_C \) is about 90°. Using this reasoning the relative configuration of the 8-substituted-6,7-benzomorphans prepared during this study were assigned on the basis of their NMR spectrum with the diastereomer possessing the larger coupling constant and the lower field absorption being assigned the \( \beta \)-substituent configuration, and the diastereomer possessing the smaller coupling constant and the higher field absorption being assigned the \( \alpha \)-substituent configuration. A summary of the coupling constants of these 8-substituted derivatives is given in Table 2.
TABLE 2
COUPLING CONSTANTS AND CHEMICAL SHIFTS OF THE
8-BENZYLIC PROTON OF 8-HYDROXY-6,7-
BENZOMORPHAN DERIVATIVES.

![Chemical structure of 8β-hydroxy-6,7-benzomorphan]

<table>
<thead>
<tr>
<th>Compound</th>
<th>R</th>
<th>R'</th>
<th>Solvent</th>
<th>$J_{HAHC}$</th>
<th>$J_{HBHC}$</th>
<th>$\delta$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-methyl-8β-hydroxy-6,7-benzomorphan (81b)</td>
<td>Me</td>
<td>H</td>
<td>CDCl$_3$</td>
<td>6.5</td>
<td></td>
<td>4.76</td>
</tr>
<tr>
<td>2-methyl-8β-hydroxy-6,7-benzomorphan·HCl (81b·HCl)</td>
<td>Me</td>
<td>H</td>
<td>D$_2$O</td>
<td>6.5</td>
<td></td>
<td>5.26</td>
</tr>
<tr>
<td>2-tosyl-8β-hydroxy-6,7-benzomorphan (92b)</td>
<td>Ts</td>
<td>H</td>
<td>CDCl$_3$</td>
<td>6.0</td>
<td></td>
<td>4.86</td>
</tr>
<tr>
<td>2-tosyl-8α-hydroxy-6,7-benzomorphan (92a)</td>
<td>Ts</td>
<td>H</td>
<td>CDCl$_3$</td>
<td>1.5</td>
<td></td>
<td>4.51</td>
</tr>
<tr>
<td>2-tosyl-8α-ethoxy-6,7-benzomorphan (96)</td>
<td>Ts</td>
<td>Et</td>
<td>CDCl$_3$</td>
<td>0.6</td>
<td></td>
<td>4.17</td>
</tr>
<tr>
<td>2-tosyl-8β-tosyloxy-6,7-benzomorphan (95)</td>
<td>Ts</td>
<td>Ts</td>
<td>CDCl$_3$</td>
<td>6.0</td>
<td></td>
<td>5.91</td>
</tr>
</tbody>
</table>
Rapoport and Masamune had reported the successful oxidation of dihydrodesoxycodeine (83) to 10- \textit{trans}-hydroxy-dihydrodesoxycodeine (84) with cold chromic acid in dilute sulfuric acid. It was hoped that the analogous 2-n-methyl-8\textalpha-hydroxy-6,7-benzomorphan (81a) could be obtained upon the similar oxidation of 2-methyl-6,7-benzomorphan (78). However, repeated attempts failed to yield any oxidized compounds.
Since no success had been achieved in obtaining the alpha-epimer of 2-methyl-8-hydroxy-6,7-benzomorphan (81a), the N-demethylation of 2-methyl-8-oxo-6,7-benzomorphan (72) was next envisioned. A search of the literature revealed numerous reported methods of N-demethylation. Each method was seemingly characterized by moderate to high yields in some systems, low yields to failure in other systems, and difficulty in predicting success in untried systems. Thus, several reported methods of N-demethylation were attempted. The Polonovski \(^{119}\) method involved converting 2-methyl-8-oxo-6,7-benzomorphan (72) to the corresponding N-oxide (85) with hydrogen peroxide. \(^{105,120}\) Subsequently, the N-oxide was heated with acetic anhydride to give the 2-acetyl-8-oxo-6,7-benzomorphan (86) which was hydrolysed to 8-oxo-6,7-benzomorphan (87) with refluxing 20 percent sulfuric acid. The reaction product was a mixture
of three components which were separable via adsorption chromatography on Silica Gel G to give only 4.3 percent of the N-demethylated compound (87). The potassium permanganate method of N-demethylation, which involved oxidizing 2-methyl-8-oxo-6,7-benzomorphan (72) with neutral potassium permanganate, afforded only a small amount of 8-oxo-6,7-benzomorphan (87) which was identified only via thin layer chromatography and not isolated. The attempted N-de-
methylation involving the conversion of 2-methyl-8-oxo-6,7-benzomorphan (72) to the 2-chlorocarbonyl-8-oxo-6,7-benzomorphan (88) followed by hydrolysis to 8-oxo-6,7-benzomorphan (87) failed since the hydrolysis could not be effected.

It was subsequently found that 2-methyl-8-oxo-6,7-benzomorphan (72) could be successfully N-demethylated via the von Braun reaction in 51 percent yield. The 2-methyl-8-oxo-6,7-benzomorphan (72) was converted smoothly to the 2-cyano-8-oxo-6,7-benzomorphan (89), and the crude cyano compound was hydrolyzed with 6 percent hydrochloric acid. The reaction product was chromatographed over Silica Gel G giving 8-oxo-6,7-benzomorphan (87) and 2-methyl-8-oxo-6,7-benzomorphan (72). The structure of 8-oxo-6,7-benzomor-
phan was assigned on the basis of the NMR and IR spectra which were consistent with the structure. However, vapor phase chromatography revealed the presence of a minor impurity which could not be removed.

Reduction of this impure 8-oxo-6,7-benzomorphan (87) with sodium borohydride\textsuperscript{111,123} gave $\beta$-hydroxy-6,7-benzomorphan (41b) with the impurity carried along. The relative configuration was assigned on the basis of the $J_{\text{HAcH}} = 6$ Hz (see Table 2).

It was considered highly desirable at this point in the synthetic schema to purify the 8-oxo-6,7-benzomorphan (87). With this objective in mind 2-acetyl-8-oxo-6,7-benzomorphan (86) was prepared by acetylating the 8-oxo-6,7-benzomorphan (87) with acetic anhydride/pyridine. The N-acetyl derivative was iden-
tified via the appearance of an amide peak in the infra-red spectrum (1650 cm\(^{-1}\)). However, the derivative could not be crystallized and subsequent work with this compound was abandoned. The 2-(3,5-dinitro)-benzoyl-8-oxo-6,7-benzomor-

\[
\begin{align*}
\text{87} & \xrightarrow{\text{Ac}_2\text{O}} \text{pyr.} \quad \text{86}
\end{align*}
\]

phan (90) was next prepared by reacting 8-oxo-6,7-benzomorphan (87) with 3,5-dinitrobenzoyl chloride. Again the derivative was identified by the appearance of the amide peak in the infra-red spectrum (1630 cm\(^{-1}\)). Although this derivative was crystalline and could be recrystallized to purity, the low yield and anticipated difficulty in removing the 3,5-dinitrobenzoyl group precluded the use of this derivative in the synthetic sequence.

\[
\begin{align*}
\text{87} & \xrightarrow{\text{3,5-dinitrobenzoyl chloride}} \text{90}
\end{align*}
\]
The preparation of 2-tosyl-8-oxo-6,7-benzomorphan (91), by heating 8-oxo-6,7-benzomorphan (87) with p-toluenesulfonyl chloride (TsCl) in aqueous sodium carbonate, was accomplished with a 63.3 percent yield to give a crystalline material which could be recrystallized to purity. The NMR and IR spectra were consistent with the proposed structure (91).

The 2-tosyl-8-oxo-6,7-benzomorphan (91) was reduced to the analytically pure 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b) with sodium borohydride. Although the earlier studies of the reduction of 2-methyl-8-oxo-6,7-benzomorphan (72) had suggested that reduction into the 8α-hydroxy system was not possible, an attempt was made to reduce 2-tosyl-8-oxo-6,7-benzomorphan (91) with aluminum isopropoxide. Aluminum isopropoxide reduction is reported to often lead to a significant amount of the sterically unfavored product. However, only the 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b) resulted from the reduction. Again, the relative configuration was assigned on the basis of $J_{HA,H_C} = 6$ Hz (see Table 2).
The N-deotosylation was effected by refluxing a solution of 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b) dissolved in tetrahydrofuran with lithium aluminum hydride. The resultant 8β-hydroxy-6,7-benzomorphan (41b), which had a $J_{HAHC} = 6$ Hz (see Table 2) and was shown not to have undergone epimerization via NMR analysis, was isolated as the hydrochloride salt in a yield of 36.3 percent. The NMR spectrum of 41b is shown in Figure 5.

Attempts at epimerizing the benzylic hydroxyl group via refluxing 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b) in either acid or base were unsuccessful.
Figure 5. NMR spectrum of $8\beta$-hydroxy-6,7-benzomorphan.
Therefore, attention was directed toward the introduction of a displacable group into position eight. The initial attempt involved the preparation of the 8-chloro derivative under Sn i conditions. The resultant product, which was presumed to contain 8α-chloro-6,7-benzomorphan (94), was never purified or characterized since attempts at displacement of the chloro group with either refluxing potassium hydroxide in ethanol or aqueous silver carbonate in an acetone co-solvent failed to yield any hydroxyl containing material (monitored via IR).
The 2-tosyl-8β-tosyloxy-6,7-benzomorphan (95) was next prepared in a 94 percent yield by reacting 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b) with tosyl chloride in pyridine at ambient temperature. The resultant product gave NMR and IR spectra consistent with the assigned structure ($J_{HAHC} = 6$ Hz, see Table 2). An attempted displacement of the 8-tosyloxy group via refluxing

\[
92b \xrightarrow{\text{TsCl}} \text{TsCl} \xrightarrow{\text{pyr}} \begin{array}{c}
\text{Tso} \\
\text{H} \\
\text{N-Ts}
\end{array}
\]

the 2-tosyl-8β-tosyloxy-6,7-benzomorphan in 0.5 normal potassium hydroxide in ethanol resulted in the formation of two products distinguishable via vapor phase chromatography. The compounds were separated via chromatography on Silica Gel G and identified by NMR analysis as 2-tosyl-8α-ethoxy-6,7-benzomorphan (96) ($J_{HBHC} = 0.6$ Hz, see Table 2) and 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b). The 2-tosyl-8α-ethoxy-6,7-benzomorphan (96) is assumed
to result from the displacement of the tosyloxy group by the ethoxide ion which would be present in a potassium hydroxide/ethanol solution. There is literature precedence to suggest that the 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b) results from simple basic hydrolysis of the tosylate which does not affect the configuration at the eighth position.

The formation of the 2-tosyl-8α-ethoxy-6,7-benzomorphan (96) indicated that the tosyloxy group could be displaced, and it was subsequently discovered that displacement occurred when 2-tosyl-8β-tosyloxy-6,7-benzomorphan (95) was refluxed with 50 percent water/acetone yielding 2-tosyl-8α-hydroxy-6,7-benzomorphan (92a). The 2-tosyl-8α-hydroxy-6,7-benzomorphan (92a) was obtained in an 89.5 percent yield and was identified via its NMR spectrum (\(J_{HBHC} = 1.5\) Hz, see Table 2).
The N-depsoylation of 2-tosyl-8α-hydroxy-6,7-benzomorphan (92a) was accomplished analogously to the N-depsoylation of 2-tosyl-8β-hydroxy-6,7-benzomorphan (92b), giving the desired 8α-hydroxy-6,7-benzomorphan (41a) in 32 percent yield. The structure of this compound (41a) was confirmed via NMR ($J_{HB\text{C}} = 1.0$ Hz see Table 2) and elemental analyses. The NMR spectrum of 41a is shown in Figure 6.
Figure 6. NMR spectrum of 8α-hydroxy-6,7-benzomorphan.
Biological Evaluation of the Stereoisomers of Phenyl-2-Piperidyl Carbinol and the Diastereomers of 8-Hydroxy-6,7-Benzomorphan

Potentiation of the norepinephrine response by the stereoisomers of phenyl-2-piperidyl carbinol. —The enhancement of in vitro responses of norepinephrine by small amounts of sympathomimetic amines has been reported in the literature.\(^{82,133}\) It has been suggested\(^{134}\) that these amines potentiate norepinephrine by inhibiting the removal of norepinephrine by uptake sites. It would be logical to expect that differences in the capacity of the various sympathomimetic amines for inhibiting norepinephrine uptake should be reflected in differing degrees of potentiation of norepinephrine responses.

Thus, experiments were conducted\(^{135}\) to determine the ability of the stereoisomers of phenyl-2-piperidyl carbinol to potentiate the contractile effect of norepinephrine on isolated rat vas deferens preparations. The results are shown in Table 3.

The results clearly show that all four stereoisomers of phenyl-2-piperidyl carbinol at a concentration of \(10^{-4}\) molar are capable of potentiating the response of norepinephrine on the rat vas deferens to a small, but significant, extent. The results also show that no stereoselectivity exists among the four isomers in the potentiation of norepinephrine.
TABLE 3

POTENTIATION OF NOREPINEPHRINE BY THE STEREOISOMERS OF PHENYL-2-PIPERIDYL CARBINOL

-\log \text{ Molar } ED_{50} \text{ of } \\
(\sim) \text{ norepinephrine} \\
\pm \text{ S.E.M.}

<table>
<thead>
<tr>
<th>Compound</th>
<th>Molar Concentration</th>
<th>Control</th>
<th>3 min after treatment</th>
<th>(a)</th>
<th>Dose Ratio</th>
<th>(b)</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1S, 2S-(\rightarrow)-phenyl-2-piperidyl carbinol</td>
<td>(10^{-4})</td>
<td>5.31 ± 0.05</td>
<td>5.77 ± 0.12</td>
<td>5</td>
<td>2.9</td>
<td>&lt;.01</td>
<td></td>
</tr>
<tr>
<td>1R, 2R-(\rightarrow)-phenyl-2-piperidyl carbinol</td>
<td>(10^{-4})</td>
<td>5.36 ± 0.02</td>
<td>5.64 ± 0.03</td>
<td>5</td>
<td>1.9</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>1S, 2R-(\rightarrow)-phenyl-2-piperidyl carbinol</td>
<td>(10^{-4})</td>
<td>5.36 ± 0.13</td>
<td>5.70 ± 0.11</td>
<td>6</td>
<td>2.2</td>
<td>&gt;.05</td>
<td></td>
</tr>
<tr>
<td>1R, 2S-(\rightarrow)-phenyl-2-piperidyl carbinol</td>
<td>(10^{-4})</td>
<td>5.31 ± 0.07</td>
<td>5.77 ± 0.09</td>
<td>6</td>
<td>2.9</td>
<td>&lt;.01</td>
<td></td>
</tr>
</tbody>
</table>

a. Number of observations.

b. Antilog \([-\log ED_{50} \text{ after treatment}) - (-\log ED_{50} \text{ before treatment}]\).

c. Significance of control \(-\log ED_{50}\) vs. treated \(-\log ED_{50}\).
Stereospecificity of catecholamine uptake by brain synaptosomes.

A stereoselective uptake of catecholamines and related phenethylamines in peripheral adrenergic test systems has been well documented. In phenethylamines possessing only one asymmetric center located at the beta carbon, the stereoselective preference is for the R-(−) configuration. A similar stereoselectivity has recently been demonstrated for the noradrenergic synaptosomes of the rat brain. Related studies also showed a preference for the S-(+)-enantiomer of amphetamine, which has the asymmetric center located at the alpha carbon of phenethylamine. Dopaminergic synaptosomes of the rat brain, however, failed to distinguish between the enantiomers of either norepinephrine or amphetamine implying a lack of stereoselectivity for catecholamine uptake by dopaminergic neurones.

Since both norepinephrine and amphetamine have only one asymmetric center, these two phenethylamines possess only two enantiomers. Phenethylamines with asymmetric centers at both the alpha and beta carbons have four enantiomers, and the comparison of the affinities of such isomers for noradrenergic and dopaminergic neurones could facilitate an understanding of steric requirements for catecholamine uptake by these two types of neurones. Since ephedrine, phenyl-2-piperidyl carbinol, and methylphenidate are phenethylamine derivatives possessing two asymmetric centers, it was desired to contrast the effects of isomers of these compounds on catecholamine uptake by synaptosomal preparations from the corpus striatum (source of dopamin-
ergic nerve terminals) and cerebral cortex (source of noradrenergic nerve terminals) of the rat. The results of the effectiveness of these compounds at inhibiting the uptake of $^3$H-norepinephrine are summarized in Tables 4, 5, and 6.

The results indicate that the ephedrine isomers had the same potency order in both the cortex and striatum, namely \((-\)-ephedrine \(>\) \((\dagger)-\)ephedrine \(>\) \((\dagger)-\)pseudoephedrine \(>\) \((-\)-pseudoephedrine). However, the ephedrine isomers were more potent and exhibited more stereoselectivity in the cortex. Also of interest was the observation that while \((\dagger)-\) and \((-\)-ephedrine showed considerably more activity in the cortex than in the striatum, \((\dagger)-\) and \((-\)-pseudoephedrine were approximately equiactive in both centers. The fact that the \((-\)-pseudoephedrine differs from \((-\)-ephedrine only via the configuration at the alpha carbon indicates that the cortical neurones are extremely stereoselective at the alpha position.

Phenyl-2-piperidyl carbinol, which in addition to its obvious similarity to ephedrine is also chemically similar to the central stimulants methylphenidate and pipradrol, gave a very different activity pattern than ephedrine. The stereoisomers of phenyl-2-piperidyl carbinol were more potent in the striatum than in the cortex and showed more stereoselectivity in the striatum than in the cortex. Of even more interest was the observation that in both the cortical and striatal regions the threo diastereomers were more potent than the erythro diastereomers, and in the striatum the 1R,2R-phenyl-2-piperidyl carbinol
<table>
<thead>
<tr>
<th>Compound</th>
<th>Absolute Configuration (β:α)</th>
<th>Cerebral Cortex</th>
<th>Corpus Striatum</th>
<th>P Value c</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-Ephedrine</td>
<td>1R:2S</td>
<td>$7.2 \times 10^{-7}$</td>
<td>$6.2 \times 10^{-6}$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>(+)-Ephedrine</td>
<td>1S:2R</td>
<td>$2.8 \times 10^{-6}$</td>
<td>$1.2 \times 10^{-5}$</td>
<td>$&lt;0.01$</td>
</tr>
<tr>
<td>(+)-Pseudoephedrine</td>
<td>1S:2S</td>
<td>$2.1 \times 10^{-5}$</td>
<td>$2.05 \times 10^{-5}$</td>
<td>$&gt;0.05$</td>
</tr>
<tr>
<td>(-)-Pseudoephedrine</td>
<td>1R:2R</td>
<td>$6.9 \times 10^{-5}$</td>
<td>$4.1 \times 10^{-5}$</td>
<td>$&gt;0.05$</td>
</tr>
</tbody>
</table>

a. $ID_{50}$ was determined from percent inhibition of 5 min uptake of $^3H(±)$-norepinephrine, 0.1 μM. Each $ID_{50}$ value represents the mean of 3 to 5 separate determinations, in each of which 4 concentrations of drug were tested in quadruplicate.

b. Relative Potency $= \frac{7.2 \times 10^{-7} M}{ID_{50} \text{ Test Drug}} \times 100$. Each value of relative potency represents the mean ± S.E.M. from 3 to 5 $ID_{50}$ determinations.

c. Student's t test.
<table>
<thead>
<tr>
<th></th>
<th>P Value&lt;sup&gt;c&lt;/sup&gt; - Cerebral Cortex</th>
<th>P Value&lt;sup&gt;c&lt;/sup&gt; - Corpus Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td>(+)-Ephedrine vs (-)-Ephedrine</td>
<td>&lt; 0.001</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>(+)-Ephedrine vs (-)-Pseudoephedrine</td>
<td>&lt; 0.05</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>(+)-Ephedrine vs (+)-Pseudoephedrine</td>
<td>&lt; 0.01</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>(-)-Ephedrine vs (-)-Pseudoephedrine</td>
<td>&lt; 0.001</td>
<td>&lt; 0.025</td>
</tr>
</tbody>
</table>
### TABLE 5

**RELATIVE POTENCY OF ISOMERS OF PHENYL-2-PIPERIDYL CARBINOL AS INHIBITORS OF 5 MIN UPTAKE OF \(^3\)H(±)-NOREPINEPHRINE IN SYNAPTOSOMES OF RAT CEREBRAL CORTEX AND CORPUS STRIATUM**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absolute Configuration (β:a)</th>
<th>Cerebral Cortex</th>
<th>Corpus Striatum</th>
<th>P Value(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>( \text{ID}_{50}(\text{M})^a )</td>
<td>Relative Potency (^b)</td>
<td>( \text{ID}_{50}(\text{M})^a )</td>
</tr>
<tr>
<td>Threo(-)-Phenyl-2-Piperidyl Carbinol</td>
<td>1R:2R</td>
<td>( 5.7 \times 10^{-5} )</td>
<td>( 1.26 \pm 0.19 )</td>
<td>( 6.4 \times 10^{-6} )</td>
</tr>
<tr>
<td>Threo(+) -Phenyl-2-Piperidyl Carbinol</td>
<td>1S:2S</td>
<td>( 5.3 \times 10^{-5} )</td>
<td>( 1.36 \pm 0.22 )</td>
<td>( 2.6 \times 10^{-5} )</td>
</tr>
<tr>
<td>Erythro(+) -Phenyl-2-Piperidyl Carbinol</td>
<td>1S:2R</td>
<td>( 2.5 \times 10^{-4} )</td>
<td>( 0.29 \pm 0.055 )</td>
<td>( 4.2 \times 10^{-5} )</td>
</tr>
<tr>
<td>Erythro(-)-Phenyl-2-Piperidyl Carbinol</td>
<td>1R:2S</td>
<td>( 2.8 \times 10^{-4} )</td>
<td>( 0.26 \pm 0.049 )</td>
<td>( 5.3 \times 10^{-5} )</td>
</tr>
</tbody>
</table>

\(^a\) Same as in Table 4.

\(^b\) Same as in Table 4.

\(^c\) Same as in Table 4.
<table>
<thead>
<tr>
<th></th>
<th>P Value&lt;sup&gt;c&lt;/sup&gt; - Cerebral Cortex</th>
<th>P Value&lt;sup&gt;c&lt;/sup&gt; - Corpus Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Threo(+) -vs Threo(-) -PPC</strong></td>
<td>&gt;0.05</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>Erythro(+) -vs Erythro(-) -PPC</strong></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td><strong>Threo(-) -vs Erythro(-) -PPC</strong></td>
<td>&lt;0.05</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td><strong>Threo(+) -vs Erythro(+) -PPC</strong></td>
<td>&lt;0.05</td>
<td>&lt;0.025</td>
</tr>
</tbody>
</table>
### Table 6

**Relative Potency of Racemates of Erythro- and Threo- Methylphenidate as Inhibitors of 5 Min Uptake of \(^3\)H(±)-Norepinephrine in Synaptosomes of Rat Cerebral Cortex and Corpus Striatum**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Absolute Configuration (\beta:alpha)</th>
<th>Cerebral Cortex</th>
<th>Corpus Striatum</th>
<th>P Value (^c) Cortex vs. Striatum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(ID_{50}(M)^a)</td>
<td>Relative Potency (^b)</td>
<td>(ID_{50}(M)^a)</td>
</tr>
<tr>
<td>Threo(±)-Methylphenidate</td>
<td>{1S:2S, 1R:2R}</td>
<td>8.5 x 10(^{-7})</td>
<td>84.0 ± 5.4</td>
<td>1.2 x 10(^{-7})</td>
</tr>
<tr>
<td>Erythro(±)-Methylphenidate</td>
<td>{1R:2S, 1S:2R}</td>
<td>1.0 x 10(^{-4})</td>
<td>0.72 ± 0.058</td>
<td>1.7 x 10(^{-5})</td>
</tr>
</tbody>
</table>

\(^a\) Same as in Table 4.
\(^b\) Same as in Table 4.
\(^c\) Same as in Table 4.

**P Value\(^c\) - Cerebral Cortex**

Threo - vs Erythro(±)-Methylphenidate \(< 0.001\)

**P Value\(^c\) - Corpus Striatum**

Threo - vs Erythro(±)-Methylphenidate \(< 0.001\)
was more potent than the $1S, 2S$-enantiomer. While these results differ quite markedly from the results obtained with the ephedrine isomers, they resemble the types of results obtained for the inhibition of norepinephrine uptake by rabbit aortic strips by the stereoisomers of methylphenidate.\textsuperscript{77}

Since the enantiomers of methylphenidate were unavailable, only the \textbf{threo} and \textbf{erythro} diastereomers were evaluated in this test system. The \textbf{threo}-methylphenidate was found to be more potent than the \textbf{erythro} diastereomer as an inhibitor of norepinephrine uptake in both the cortical and striatal fractions. This observation is similar to the results obtained by Szporny and Gorog\textsuperscript{82} who tested methylphenidate as a central stimulant and noted that the \textbf{threo} diastereomer was a more potent central stimulant than the \textbf{erythro} diastereomer. Also, as in the case of the phenyl-2-piperidyl carbinols, the methylphenidates were more potent in the striatum than in the cortex.

The results obtained may be explained in several possible ways. Since phenyl-2-piperidyl carbinol and methylphenidate give the same type of stereo-selectivity pattern it seems feasible to suggest that their inhibition of $^3$H-norepinephrine uptake involves the same procedure. One could suggest that the addition of the two methylene groups to the amino side chain in phenyl-2-piperidyl carbinol and methylphenidate could sterically affect drug-receptor interactions causing the observed differences between the inhibitory effects of the ephedrines and the phenyl-2-piperidyl carbinols and methylphenidates in the cortical and striatal fractions, or that the observed differences could be
due to solubility differences. On the other hand, the observed differences could be due to the ephedrines and the phenyl-2-piperidyl carbinols and methyl-phenidates eliciting their inhibitory effects by entirely different methods, for example, interacting with different allosteric sites.

**Lipolysis studies with the ephedrine isomers, the phenyl-2-piperidyl carbinol isomers, and the 8-hydroxy-6,7-benzomorphan diastereomers.**

The role of catecholamines in the mobilization of free-fatty acid has been well documented. In recent years several investigators have studied the ability of numerous phenethylamine derivatives to induce the mobilization of free-fatty acids. However, most of the work to date has involved the investigation of catechol or monophenolic derivatives, with only a brief mention made of nonphenolic phenethylamines. Feller and Finger reported that racemic phenylpropanolamine was somewhat effective in inducing lipolysis while racemic ephedrine, phenethylamine, and (±)-amphetamine were ineffective in inducing lipolysis. Other studies, involving the use of adrenergic blocking agents, have demonstrated that lipolysis can be inhibited.

In an effort to extend the knowledge of the effects of phenethylamines on lipolysis, several nonphenolic derivatives, namely the isomeric ephedrine, the isomeric phenyl-2-piperidyl carbinols, and the diastereomeric 8-hydroxy-6,7-benzomorphans were evaluated as lipolysis agonists and antagonists of
norepinephrine induced lipolysis in the in vitro procedure of Finger and co-workers. This procedure involved inducing (or blocking the norepinephrine inducement of) the hydrolysis of stored fat in rat epididymal fat pads into glycerol and free-fatty acid and subsequently assaying the released glycerol as a monitor of lipolysis.

It was found that none of the ten compounds functioned as agonists in inducing the mobilization of free-fatty acid at concentrations of $10^{-3}$, $10^{-4}$, and $10^{-5}$ M. This evidence extends the earlier observation that (±)-ephedrine failed to induce lipolysis to include the fact that no induced lipolysis is observed for the ephedrine isomers, the phenyl-2-piperidyl carbinol isomers, and the 8-hydroxy-6,7-benzomorphinan diastereomers. Also, this evidence supports the contention that either the catechol nucleus or a monophenolic substituent is necessary for optimal agonist activity.

However, when the compounds were tested as inhibitors of norepinephrine induced lipolysis (Table 7) an interesting and consistent pattern developed. Figure 7, which shows the plot of percent inhibition of lipolysis against the negative logarithm of the molar concentration of the ephedrine isomers, reveals that all four stereoisomers of ephedrine function as antagonists with the potency order being $1R, 2S$-(-)-ephedrine > $1S, 2R$-(+)-ephedrine > $1S, 2S$-(+)-pseudoephedrine > $1R, 2R$-(-)-pseudoephedrine. Table 8 reveals that $1R, 2S$-(−)-ephedrine is about 30 times more potent than the other ephedrine isomers.

Upon examination of Figure 8 it becomes obvious that the same types of
TABLE 7
PERCENT INHIBITION OF NOREPINEPHRINE INDUCED LIPOLYSIS
BY THE ISOMERS OF EPHEDRINE, THE ISOMERS OF
PHENYL-2-PIPERIDYL CARBINOL, AND THE
DIASTEREOMERS OF 8-HYDROXY-6, 7-
BENZOMORPHAN

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conc. (M)</th>
<th>n</th>
<th>% Inhibition ± S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1R, 2S-(−)-ephedrine</td>
<td>$10^{-3}$</td>
<td>5</td>
<td>98.5 ± 0.4</td>
</tr>
<tr>
<td></td>
<td>$10^{-4}$</td>
<td>5</td>
<td>86.5 ± 3.0</td>
</tr>
<tr>
<td></td>
<td>$10^{-5}$</td>
<td>4</td>
<td>45.0 ± 5.5</td>
</tr>
<tr>
<td></td>
<td>$10^{-6}$</td>
<td>3</td>
<td>16.9 ± 7.5</td>
</tr>
<tr>
<td>1S, 2R-(+)-ephedrine</td>
<td>$10^{-3}$</td>
<td>5</td>
<td>75.2 ± 4.5</td>
</tr>
<tr>
<td></td>
<td>$10^{-4}$</td>
<td>4</td>
<td>24.6 ± 6.6</td>
</tr>
<tr>
<td></td>
<td>$10^{-5}$</td>
<td>4</td>
<td>9.0 ± 7.8</td>
</tr>
<tr>
<td></td>
<td>$10^{-6}$</td>
<td>3</td>
<td>5.2 ± 4.2</td>
</tr>
<tr>
<td>1R, 2R-(−)-Ψ-ephedrine</td>
<td>$10^{-3}$</td>
<td>3</td>
<td>64.0 ± 6.4</td>
</tr>
<tr>
<td></td>
<td>$10^{-4}$</td>
<td>3</td>
<td>14.0 ± 11.0</td>
</tr>
<tr>
<td></td>
<td>$10^{-5}$</td>
<td>3</td>
<td>8.7 ± 2.2</td>
</tr>
<tr>
<td>1S, 2S-(+)-Ψ-ephedrine</td>
<td>$10^{-3}$</td>
<td>3</td>
<td>66.5 ± 3.6</td>
</tr>
<tr>
<td></td>
<td>$10^{-4}$</td>
<td>3</td>
<td>14.8 ± 8.0</td>
</tr>
<tr>
<td></td>
<td>$10^{-5}$</td>
<td>3</td>
<td>6.8 ± 5.5</td>
</tr>
<tr>
<td>1R, 2S-(−)-PPC b</td>
<td>$10^{-3}$</td>
<td>4</td>
<td>86 ± 5</td>
</tr>
<tr>
<td></td>
<td>$3.16 \times 10^{-4}$</td>
<td>3</td>
<td>72 ± 1</td>
</tr>
<tr>
<td></td>
<td>$10^{-4}$</td>
<td>13</td>
<td>60 ± 3</td>
</tr>
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<td></td>
<td>$3.16 \times 10^{-5}$</td>
<td>3</td>
<td>27 ± 3</td>
</tr>
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<td></td>
<td>$10^{-5}$</td>
<td>4</td>
<td>14 ± 4</td>
</tr>
<tr>
<td>1S, 2R-(+)-PPC</td>
<td>$10^{-3}$</td>
<td>4</td>
<td>61 ± 3</td>
</tr>
<tr>
<td></td>
<td>$3.16 \times 10^{-4}$</td>
<td>3</td>
<td>28 ± 3</td>
</tr>
<tr>
<td></td>
<td>$10^{-4}$</td>
<td>3</td>
<td>14 ± 7</td>
</tr>
<tr>
<td></td>
<td>$10^{-5}$</td>
<td>4</td>
<td>6 ± 5</td>
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</table>
### TABLE 7—Continued

<table>
<thead>
<tr>
<th>Compound</th>
<th>Conc. (M)</th>
<th>n(^a)</th>
<th>% Inhibition ± S.E.M.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1S, 2S-(+)-PPC</td>
<td>10(^{-3})</td>
<td>4</td>
<td>46 ± 3</td>
</tr>
<tr>
<td></td>
<td>3.16 x 10(^{-4})</td>
<td>3</td>
<td>24 ± 6</td>
</tr>
<tr>
<td></td>
<td>10(^{-4})</td>
<td>3</td>
<td>13 ± 4</td>
</tr>
<tr>
<td></td>
<td>10(^{-5})</td>
<td>3</td>
<td>6 ± 6</td>
</tr>
<tr>
<td>8β-HBM(^c)</td>
<td>10(^{-3})</td>
<td>3</td>
<td>54 ± 7</td>
</tr>
<tr>
<td></td>
<td>3.16 x 10(^{-4})</td>
<td>3</td>
<td>33 ± 3</td>
</tr>
<tr>
<td></td>
<td>10(^{-4})</td>
<td>3</td>
<td>20 ± 7</td>
</tr>
<tr>
<td></td>
<td>10(^{-5})</td>
<td>3</td>
<td>16 ± 7</td>
</tr>
<tr>
<td>8α-HBM</td>
<td>10(^{-3})</td>
<td>3</td>
<td>13 ± 3</td>
</tr>
<tr>
<td></td>
<td>3.16 x 10(^{-4})</td>
<td>3</td>
<td>9 ± 5</td>
</tr>
<tr>
<td></td>
<td>10(^{-4})</td>
<td>3</td>
<td>3 ± 1</td>
</tr>
<tr>
<td></td>
<td>10(^{-5})</td>
<td>3</td>
<td>2 ± 1</td>
</tr>
</tbody>
</table>

\(a\). Number of observations

\(b\). phenyl-2-piperidyl carbinol.

\(c\). hydroxy-6,7-benzomorphan.
Figure 7. The inhibition of norepinephrine induced lipolysis by the isomers of ephedrine.
PERCENT INHIBITION

![Graph showing percent inhibition against concentration.](image-url)
TABLE 8

RELATIVE POTENCY OF THE ISOMERS OF EPHEDRINE, THE ISOMERS OF PHENYL-2-PIPERIDYL CARBINOL, AND THE DIASTEREOMERS OF 8-HYDROXY-6, 7-BENZOMORPHAN AS INHIBITORS OF NOREPINEPHRINE INDUCED LIPOLYSIS

<table>
<thead>
<tr>
<th>Compound</th>
<th>ID$_{50}$a</th>
<th>Relative Potency$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1R, 2S-(−)-ephedrine</td>
<td>1.3 x 10$^{-5}$</td>
<td>100</td>
</tr>
<tr>
<td>1S, 2R-(+)-ephedrine</td>
<td>4.0 x 10$^{-4}$</td>
<td>3.2</td>
</tr>
<tr>
<td>1R, 2R-(−)-pseudoephedrine</td>
<td>6.3 x 10$^{-4}$</td>
<td>2.1</td>
</tr>
<tr>
<td>1S, 2S-(+)-pseudoephedrine</td>
<td>6.3 x 10$^{-4}$</td>
<td>2.1</td>
</tr>
<tr>
<td>1R, 2S-(−)-PPC</td>
<td>6.3 x 10$^{-5}$</td>
<td>20.6</td>
</tr>
<tr>
<td>1S, 2R-(+)-PPC</td>
<td>&gt;1 x 10$^{-3}$</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td>1R, 2R-(−)-PPC</td>
<td>6.3 x 10$^{-4}$</td>
<td>2.1</td>
</tr>
<tr>
<td>1S, 2S-(+)-PPC</td>
<td>&gt;1 x 10$^{-3}$</td>
<td>&lt;1.3</td>
</tr>
<tr>
<td>8β-HBM</td>
<td>7.9 x 10$^{-4}$</td>
<td>1.6</td>
</tr>
<tr>
<td>8α-HBM</td>
<td>≫1 x 10$^{-3}$</td>
<td>≪1.3</td>
</tr>
</tbody>
</table>

a. ID$_{50}$ was obtained from the plot of percent inhibition against -log M.

b. Relative Potency = $\frac{1.3 \times 10^{-5}}{\text{ID}_{50}} \times 100$. 
Figure 8. The inhibition of norepinephrine induced lipolysis by the isomers of phenyl-2-piperidyl carbinol.
effects are being observed for the stereoisomers of phenyl-2-piperidyl carbinol. All four stereoisomers can be seen to again inhibit norepinephrine induced lipolysis, and, again, the inhibition can be seen to be stereoselective with the potency order being 1R, 2S-(−)-phenyl-2-piperidyl carbinol > 1R, 2R-(−)-phenyl-2-piperidyl carbinol > 1S, 2S-(−)-phenyl-2-piperidyl carbinol > 1S, 2R-(−)-phenyl-2-piperidyl carbinol. Table 8 reveals that the most active phenyl-2-piperidyl carbinol, namely the 1R, 2S-isomer, is only about one-fifth as potent as the most active ephedrine isomer, (−)-ephedrine. Also, the phenyl-2-piperidyl carbinols are not as stereoselective in their receptor interaction as are the ephedrine isomers since the 1R, 2S-phenyl-2-piperidyl carbinol can be seen in Table 8 to be only about 10 times more potent than the other phenyl-2-piperidyl carbinols.

Examination of models of the benzomorphans reveals that the 8β-hydroxy-6,7-benzomorphan is a conformationally rigid compound coinciding with the erythro configuration while the 8α-hydroxy-6,7-benzomorphan is a conformationally rigid compound coinciding with the threo configuration. It can be seen in Figure 9 that the 8β-hydroxy derivative is more active than the 8α-hydroxy derivative, thus, although both diastereomers possessed inhibitory activity the erythro configuration possessed the more activity just as in the case of the ephedrine and the phenyl-2-piperidyl carbinol isomers. Table 8 reveals that the 8β-hydroxy diastereomer is about one-sixtieth as active as an inhibitor as
Figure 9. The inhibition of norepinephrine induced lipolysis by the diastereomers of 8-hydroxy-6,7-benzomorphan.
PERCENT INHIBITION

-log10 M

HBM

20
0
80
100
1R, 2S-(−)-ephedrine and about one-thirteenth as active as 1R, 2S-(−)-phenyl-2-piperidyl carbinol.

The data seems to suggest that the nonphenolic phenethylamines, ephedrine, phenyl-2-piperidyl carbinol, and 8-hydroxy-6,7-benzomorphan possess affinity for the receptor associated with lipolysis, but lack an intrinsic activity. The erythro configuration in the form of the 1R, 2S-enantiomers seems to be best accommodated by the receptor. The conformation which is associated with 8β-hydroxy-6,7-benzomorphan is better accommodated than the conformation associated with 8α-hydroxy-6,7-benzomorphan. There appears to be two possible explanations for the potency difference between 1R, 2S-(−)-ephedrine and 1R, 2S-(−)-phenyl-2-piperidyl carbinol. Since the phenyl-2-piperidyl carbinol molecule contains two more methylene groups than ephedrine, the potency difference could be explained by lipid solubility changes or by steric interferences due to the added methylene groups. Alternatively, the potency difference may be attributable to the receptor more easily accommodating α-methyl and N-methyl groups in a spatial arrangement which can be assumed in ephedrine than in the somewhat restricted piperidine ring of phenyl-2-piperidyl carbinol.

The 8-hydroxy-6,7-benzomorphan molecule is a particularly attractive rigid analog of phenyl-2-piperidyl carbinol since it contains no more added atoms. Thus, an equivalent activity between phenyl-2-piperidyl carbinol and 8-hydroxy-6,7-benzomorphan might, in fact, suggest the conformation assumed
by phenyl-2-piperidyl carbinol is the same as the conformation fixed in 8-hydroxy-6,7-benzomorphan. The potency differences between phenyl-2-piperidyl carbinol and 8-hydroxy-benzomorphan is in part explainable by the fact that the benzomorphans were tested as diastereomers.
**EXPERIMENTAL**

**Synthetic**

*General.*—Melting points were determined in open capillaries on a Thomas-Hoover Uni-Melt apparatus and are uncorrected. The circular dichroism measurements were carried out using a Durrum-Jasco Model ORD/UV-5 instrument equipped with a c.d. attachment operating at ambient temperature. Infrared spectra were obtained with a Perkin-Elmer Model 257 or Model 237 grating spectrophotometer. The NMR spectra were recorded with a Varian A-60A NMR spectrometer at 60 MHz. Vapor phase chromatographs were taken using a F & M Model 402 gas chromatograph equipped with flame ionizing detector and glass columns. Elemental analyses were determined by Alfred Bernhardt Microanalytical Laboratory, Fritz-Pregl-Strasse 14-16, West Germany.

**Phenyl-2-pyridyl carbinol (43).**—Method A: Platinum oxide (Matheson Coleman and Bell) (0.100 g) was placed in water (10 ml) and shaken on a Parr Hydrogenator under an initial hydrogen pressure of 20 pounds per square inch until the brown oxide was reduced to the black platinum (required about 30 minutes). To the reaction bottle was added phenyl-2-pyridyl ketone (Aldrich)
(10 g, 0.055 mol), hydrochloric acid (10.7 ml), and water (45 ml). The reduction was allowed to proceed at room temperature and an initial pressure of 41 pounds per square inch until no further hydrogen uptake occurred (24 hrs). The catalyst was removed via filtration, and the solvent was removed under vacuum leaving a pale yellow viscous liquid: yield 7.50 g. The oil was crystallized by dissolving it in anhydrous ethanol (37 ml) and adding anhydrous ether (225 ml). The crystalline material was recrystallized via the same method yielding a white crystalline hydrochloride salt: yield 2.60 g (22.2%); mp 184-185.5°.

**Anal.** Calcd for C\textsubscript{12}H\textsubscript{12}ONCl: C, 65.00; H, 5.50; N, 6.40. Found: C, 65.11; H, 5.40; N, 6.38.

**Method B:** Phenyl-2-pyridyl ketone (3.2 g, 0.017 mol) was dissolved in anhydrous ethanol (30 ml) and cooled in an ice bath. To this solution was slowly added clean sodium metal (4.7 g) followed by additional anhydrous ethanol (15 ml). The reaction mixture was allowed to warm to room temperature then heated on an oil bath until the sodium had dissolved. The excess sodium was decomposed by slowly adding water. The solvent was removed under vacuum and the resultant dark oil was dissolved in ether, acidified with hydrogen chloride gas, and crystallized by dissolving the gummy hydrochloride salt in anhydrous ethanol (10 ml) and adding anhydrous ether (70 ml). Three additional recrystallizations from the same solvent system gave the white crystalline hydrochloride salt: yield 0.410 g (10.6%); mp 183.5-185°.
Phenyl-2-piperidyl carbinol (40).—Method A: Brown catalyst was generated "in situ" by placing a 0.2 molar chloroplatinic acid solution (2 ml), activated carbon (Darco) (2 g), and anhydrous ethanol (25 ml) in a 250 ml Brown reaction flask and adding to this with stirring 1.0 molar alcoholic sodium borohydride (10 ml) followed 1 min later by concentrated hydrochloric acid (8 ml). To this mixture was added phenyl-2-pyridyl ketone (9.15 g, 0.05 mol) dissolved in concentrated hydrochloric acid (10 ml) and anhydrous ethanol (10 ml). The reaction flask was then attached to the Brown Hydrogenator (Delmar) assembled for external hydrogen generation, the system was flushed with hydrogen, and the reaction was allowed to proceed until no further hydrogen uptake was observed. The reduction required 10 hrs and 45.8 ml of the 1.0 molar sodium borohydride solution were consumed (theoretical, 50.0 ml). The catalyst was removed via filtration, and the solvent was removed under vacuum leaving a tacky oil which was dissolved in hot anhydrous ethanol (45 ml) and precipitated with anhydrous ether (270 ml). The crystalline erythro-phenyl-2-piperidyl carbinol (40a) hydrochloride was removed via filtration and the mother liquor set aside as solution A. The hydrochloride salt was recrystallized 3 times from anhydrous ethanol (22.5 ml) and anhydrous ether (135 ml): yield 1.8 g (16%); mp 202-203° (lit. 200-203°). The hydrochloride salt was dissolved in water (20 ml) and made basic with 10 percent sodium hydroxide. The resultant solid was removed via filtration and recrystallized from 50 percent ethanol/water: yield 1.5 g; mp 140-142° (lit. 141-.
nmr (see Figure 1) (DOAc) δ 1.78 (m, 6, methylene protons) 3.47 (m, 3, methylene and methine protons adjacent to nitrogen) 5.20 (d, 1, benzylic proton, J = 3.3 Hz) 7.34 (s, 5, aromatic protons).

Solution A was taken to dryness under vacuum, and the resultant three-phenyl-2-piperidyl carbinol (40b) hydrochloride was dissolved in water (20 ml) and made basic with 10 percent potassium hydroxide. The solid which formed was removed via filtration and recrystallized 4 times from 50 percent ethanol/water: yield 1.1 g (12%); mp 170-173° (lit. 171-173°); nmr (see Figure 2) (DOAc) δ 1.72 (m, 6, methylene protons) 3.42 (m, 3, methylene and methine protons adjacent to nitrogen) 4.80 (d, 1, benzylic proton, J = 9.3 Hz) 7.36 (s, 5, aromatic protons).

Method B: Brown catalyst was generated "in situ" in a Parr bottle as described under Method A. To this catalyst was added phenyl-2-pyridyl ketone (9.15 g, 0.05 mol), concentrated hydrochloric acid (10 ml), and anhydrous ethanol (10 ml). The reduction was conducted at ambient temperature and an initial pressure of 42 pounds per square inch. The uptake of hydrogen was complete in 11 1/2 hrs. The reduction product was worked up as in Method A giving 40a: yield 1.38 g (14.6%); mp 140-142° and 40b: yield 1.20 g (12.6%); mp 170-173°.

Resolution of erythro-phenyl-2-piperidyl carbinol (40a).—A solution of erythro-phenyl-2-piperidyl carbinol (2.0 g, 0.01 mol) and (±)-mandelic acid (Aldrich) (1.2 g, 0.008 mol) in hot 95 percent ethanol (8 ml) was allowed to
slowly cool to room temperature. The crystals which separated were removed via filtration and the mother liquor set aside as solution A. The crystals were recrystallized twice from 95 percent ethanol (4 ml): mp 145-146\(^\circ\). A solution of these crystals in water (25 ml) was made basic with 10 percent potassium hydroxide, extracted with ether (4 x 20 ml), and dried (magnesium sulfate). The ether volume was reduced to about 20 ml and made acidic with gaseous hydrogen chloride. The resultant hydrochloride salt (40d·HCl) was collected via filtration: yield 0.278 g (11.6%); mp 213.5-215\(^\circ\); \([\alpha]_{D}^{25} = +23.1\)^0 (water).

Solution A was taken to dryness and the free base regenerated as described above. The resultant free base was combined with (-)-mandelic acid (Aldrich) (1.2 g, 0.008 mol) in hot 95 percent ethanol (4 ml). The solution was allowed to cool slowly to room temperature, and the crystals were removed via filtration and recrystallized twice from 95 percent ethanol (4 ml): mp 144-146\(^\circ\). The free base was regenerated and converted to the hydrochloride salt (40c·HCl) as described above: yield 0.464 g (22.3%); \([\alpha]_{D}^{25} = -22.0\)^0 (water).

**Resolution of threo-phenyl-2-piperidyl carbinol (40b).**—A solution of threo-phenyl-2-piperidyl carbinol (1.0 g, 5 mmol) and (+)-di-p-toluoyl-tartaric acid (Aldrich) (1.3 g, 3.4 mmol) in hot ethanol (2 ml) was allowed to come slowly to room temperature. The crystals which formed were removed via filtration and the mother liquor set aside as solution B. The crystals were recrystallized 5 times from 50 percent butanol/ethanol: mp 185-186\(^\circ\). The free
base was regenerated as above, the ether volume was reduced to about 20 ml, and the free base (40c) precipitated (could not prepare the hydrochloride salt): yield 0.118 g (11.8%); mp 149-151°; $[\alpha]_D^{25} = -15.9^\circ$ (ethanol).

Solution B was taken to dryness and the free base regenerated as above. The resultant solid and (-)-di-p-toluoyl-tartaric acid (Aldrich) (0.845 g, 2.2 mmol) were dissolved in hot ethanol (2 ml). The crystals which formed upon cooling slowly to room temperature were removed via filtration and recrystallized 5 times from 50 percent butanol/ethanol: mp 185-186°. The free base was regenerated as above (40d): yield 0.132 g (13.2%); mp 149-151°; $[\alpha]_D^{25} = +16.2^\circ$ (ethanol).

Circular dichroism measurements. --(1R, 2S)-Phenyl-2-piperidyl carbinol (40c). --Circular dichroism measurements were made at 5.23 x 10^{-5} M (ethanol): $[\theta]_273 = 0$, $[\theta]_268 = 757$, $[\theta]_266 = 252$, $[\theta]_261 = 821$, $[\theta]_258 = 442$, $[\theta]_255 = 537$, $[\theta]_250 = 284$, $[\theta]_248 = 252$, $[\theta]_246 = 158$.

(1S, 2R)-Phenyl-2-piperidyl carbinol (40d). --Circular dichroism measurements were made at 5.23 x 10^{-5} M (ethanol): $[\theta]_274 = 0$, $[\theta]_268 = -789$, $[\theta]_265 = -347$, $[\theta]_261 = -884$, $[\theta]_257 = -442$, $[\theta]_255 = -537$, $[\theta]_250 = -252$, $[\theta]_246 = -158$.

(1R, 2R)-Phenyl-2-piperidyl carbinol (40e). --Circular dichroism measurements were made at 6.55 x 10^{-5} M (ethanol): $[\theta]_274 = 0$, $[\theta]_268 = 434$, $[\theta]_265 = 152$, $[\theta]_261 = 455$, $[\theta]_257 = 283$, $[\theta]_256 = 354$, $[\theta]_251 = 202$, $[\theta]_250 = 222$, $[\theta]_245 = 91$, $[\theta]_243 = 101$. 

4-Phenylpyridine N-oxide (65). 103, 105—4-Phenylpyridine (Aldrich) (7.8 g, 0.05 mol), glacial acetic acid (30 ml), and 30 percent hydrogen peroxide (5.8 ml) were heated together on a water bath at 70-80° for 3.5 hrs. Additional 30 percent hydrogen peroxide (4.1 ml) was added and the heating was continued for 10 hrs. The heat was removed and the reaction mixture was allowed to stand at room temperature overnight. The solution was concentrated under vacuum to yield a small volume of orange oil which was diluted with water (100 ml), strongly basified with 10 percent sodium hydroxide, extracted with chloroform (3 x 150 ml), and dried (magnesium sulfate). The chloroform was removed under vacuum: yield 8.16 g (96%); mp 148-152° (lit. 103 148-149°).

1-Methoxy-4-phenylpyridinium methyl sulfate (66). 103—To 4-phenylpyridine N-oxide (31.4 g, 0.18 mol) in a 250 ml three necked flask equipped with a thermometer, a motor driven stirrer, and a dropping funnel was added dimethyl sulfate (19.1 ml, 0.20 mol). The addition required 75 min and occasional heat was needed to prevent solidification. (Note: the temperature was never allowed to exceed 70° since the reaction mixture had been reported to explode at 140°). After the addition was completed the viscous liquid was heated at 90° for an additional 2 hrs, cooled to room temperature, poured into
an evaporating dish, and allowed to solidify into an amorphous solid in a vacuum oven: yield 53.3 g (97.3%).

2-Cyano-4-phenylpyridine (67). \(^{103,144}\) -- A solution of 1-methoxy-4-phenylpyridinium methyl sulfate (53.3 g, 0.18 mol) in water (65 ml) was added slowly to a solution of sodium cyanide (26.8 g, 0.55 mol) in water (160 ml) with stirring and cooling to \(-5^\circ\) in an ice-salt-water bath. The reaction mixture was maintained at \(-5^\circ\) for an additional 45 min then allowed to come slowly to room temperature over a 2 1/2 hr period. The resultant bright yellow slurry was extracted with chloroform (3 x 100 ml) and dried (magnesium sulfate). The chloroform was removed under vacuum giving a white solid which was recrystallized from ethanol: yield 19.2 g (64.8%); mp 98-100° (lit. \(^{103}\) 99°); ir, cm

\(^{-1}\) (CHCl₂), 2251 (CN).

2-Carbomethoxy-4-phenylpyridine (68). \(^{103,145}\) -- 2-Cyano-4-phenylpyridine (3.0 g, 0.017 mol) was dissolved in methanol (50 ml) which had been saturated with hydrogen chloride gas. This solution was refluxed for 12 hrs, concentrated under vacuum to about 15 ml, and poured into water (50 ml). This solution was made basic with ammonium hydroxide and extracted with chloroform (3 x 25 ml). The combined chloroform fractions were dried (magnesium sulfate), and the solvent was removed under vacuum leaving a nearly clear oil as shown via VPC analysis: yield 3.56 g (100%).
1-Methyl-2-carbomethoxy-4-phenylpyridinium iodide (69). 103 — A solution of 1-methyl-2-carbomethoxy-4-phenylpyridine (7.5 g, 0.035 mol), acetone (30 ml), and methyl iodide (2.5 ml, 0.032 mol) was allowed to stand overnight at room temperature, diluted with ethyl acetate (15 ml), and cooled to -68° in an acetone-dry ice bath. The brown crystals which formed were removed via filtration: yield 6.13 g (48%); mp 136-140° (lit. 103 140-142°).

1-Methyl-2-carbomethoxy-4-phenylpiperidine (70). 103 — Platinum oxide (0.100 g) and methanol (10 ml) were placed in a Parr Hydrogenator and the catalyst saturated with hydrogen. A solution of 1-methyl-2-carbomethoxy-4-phenylpyridinium iodide (2.1 g, 0.006 mol) in methanol (40 ml) was added, and the hydrogenation was allowed to proceed at an initial pressure of 35 pounds per square inch and ambient temperature. Within 24 hrs a quantitative uptake of hydrogen had occurred. The catalyst was removed via filtration, and the solvent was removed under vacuum leaving a foamy yellow residue which was dissolved in water (100 ml), made basic with sodium bicarbonate, extracted with chloroform (4 x 100 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving an orange oil: yield 1.45 g (100%).

1-Methyl-2-carboxy-4-phenylpiperidine (71). 103 — A solution of 1-methyl-2-carbomethoxy-4-phenylpiperidine (1.35 g, 0.006 mol) in concentrated hydrochloric acid was refluxed for 10 hrs and evaporated under vacuum leaving the solid hydrochloride. Recrystallization from hot acetone gave a white crystal-
line material: yield 0.88 g (58.3%); mp 237.5-238° (lit. 237-238°).

2-Methyl-8-oxo-6,7-benzomorphan (72). \textsuperscript{103} --1-Methyl-2-carboxy-4-phenylpiperidine hydrochloride (7.0 g, 0.027 mol) and polyphosphoric acid (100 g) were combined and heated at 145-155° for 15 hrs. The resulting dark solution was cooled, basified with 20 percent potassium hydroxide, extracted with chloroform (3 x 300 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a brown oil: yield 4.4 g. Short path distillation gave a pale yellow oil: yield 0.60 g (11%); bp \( \_24 = 90-95° \); ir, cm\(^{-1}\) (neat), 1676 (C=O). A small amount of the distillate was combined with an excess of a saturated solution of picric acid in acetone. The picrate was removed via filtration and washed with cold acetone and warm ethanol: mp 194.5-195° (lit. 194°).

1-Methylpyridinium iodide (74). \textsuperscript{103} --To a stirred solution of pyridine (79 ml, 0.98 mol) in acetone (500 ml) was slowly added methyl iodide (62 ml, 1.0 mol). The solution was stirred for an additional 1 1/2 hrs during which time a white precipitate formed. The reaction mixture was cooled to 4°, filtered, the crystals washed with ether, and dried in a vacuum oven: yield 181.6 g (83%).

1-Methyl-1,2,5,6-tetrahydropyridine (75). \textsuperscript{103} --To a stirred solution of 1-methylpyridinium iodide (58 g, 0.26 mol) in 1 normal sodium hydroxide (300 ml) in a 1 liter 3-necked flask equipped with a mechanical stirrer was slowly
added sodium borohydride (11 g, 0.29 mol). Heat and gas evolution occurred during the addition which required about 30 min. Additional 1 normal sodium hydroxide (200 ml) was added, the reaction flask was equipped with a reflux condenser and a ground glass stopper, and the solution was heated an additional 3 hrs at 60-80°. The solution was then cooled in an ice bath, saturated with sodium chloride, extracted with ether (3 x 300 ml), and dried (magnesium sulfate). The solvent was removed on a steam bath leaving a green oil: yield 16.7 g (65.7%).

**1-Benzyl-1-methyl-1,2,5,6-tetrahydropyridinium chloride (76).** --To a stirred solution of 1-methyl-1,2,5,6-tetrahydropyridine (76.4 g, 0.79 mol) in acetone (300 ml) was slowly added benzyl chloride (91.2 g, 0.73 mol). The solution was stirred at room temperature for 2 hrs during which time precipitation occurred. The hygroscopic solid was removed via filtration and dried in a vacuum oven: yield 144.7 g (81.9%).

**1-Methyl-2-benzyl-1,2,5,6-tetrahydropyridine (77).** --The phenyl lithium was prepared according to the procedure of Vogel. A 500 ml 3-necked flask containing lithium wire (3.68 g) in ether (25 ml) was equipped with a mercury-sealed stirrer, dropping funnel, and a reflux condenser and flushed with nitrogen. To this mixture a solution of bromobenzene (26.3 ml) in ether (100 ml) was added at such a rate as to maintain gentle reflux. Additional ether (25 ml) was added and the mixture stirred for 5 hrs until most of
the lithium had dissolved. The solution was 1.7 molar.

To 1-methyl-1-benzyl-1,2,5,6-tetrahydropyridinium chloride (144.7 g, 0.62 mol) as a dry powder was added the ethereal 1.7 molar phenyl lithium (515 ml, 1.4 equivalents). Benzene (300 ml) was added at intervals over 4 hrs to increase solubility. The reaction mixture was poured into ice-water, and the aqueous layer was extracted with benzene (4 x 200 ml). The combined organic phase was extracted with an excess of 10 percent hydrochloric acid, and the aqueous phase washed with dichloromethane. The aqueous phase was made basic with concentrated ammonium hydroxide, extracted with ether (3 x 100 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a red-brown oil: yield 55.9 g. This oil was fractionally distilled: yield 15.1 g (12.5%); bp. 70-75°.

2-Methyl-6,7-benzomorph (78).—A stirred solution of 1-methyl-1,2,5,6-tetrahydropyridine (13.0 g, 0.07 mol) in polyphosphoric acid (450 g) was heated for 45 hrs on an oil bath maintained at 150-160°. After cooling and decomposing with ice-water, the reaction mixture was made basic with concentrated ammonium hydroxide, extracted with dichloromethane (5 x 300 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a dark oil which was fractionated: yield 4.4 g; bp. 67-70°. The fractionated oil was dissolved in ether and made acidic with gaseous hydrogen chloride giving a gummy white solid. After 2 recrystallizations from acetone (3)/methanol
(3)/ether (20), the crystalline hydrochloride was obtained: yield 2.66 g (17.1%); mp 222-223.5° (lit. 224-225°); nmr (CDCl₃) δ 2.39 (s, 1, N-Me) 7.06 (s, 4, aromatic protons) 1.19-3.37 (broad methylene-methine envelope, 10).

6,7-Benzomorphan (79).—Method A: A solution of 2-methyl-6,7-benzomorphan (0.168 g, 0.9 mmol), diethylazodicarboxylate (0.200 g, 1.1 mmol), and chloroform (10 ml) was refluxed for 4 hrs, cooled, and the solvent was removed under vacuum. The residue, pyridine hydrochloride (0.15 g), water (5 ml), and ethanol (10 ml) were allowed to stand at room temperature for 14 hrs, made basic with 10 percent sodium hydroxide, extracted with chloroform (4 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving an orange oil which was dissolved in a saturated solution of picric acid in acetone (3 ml). After several days the yellow solid was removed via filtration and recrystallized from hot ethanol: yield 0.171 g; mp 161-165° (lit. 171-173°). The free base was regenerated by dissolving the picrate in hot benzene (100 ml) and adding ammonium hydroxide (25 ml). The aqueous phase was washed with benzene (25 ml) and the combined organic phase was dried (magnesium sulfate). The solvent was removed under vacuum: yield 0.058 g (38.2%).

Method B: A solution of 2-methyl-6,7-benzomorphan (0.187 g, 1 mmol) in chloroform (5 ml) was added slowly to a stirred solution of cyanogen bromide (0.120 g, 1.1 mmol) in chloroform (5 ml). The solution was refluxed
for 2 hrs and evaporated to dryness under vacuum. The residue and 6 percent hydrochloric acid (15 ml) were refluxed for 44 hrs, cooled, made basic with ammonium hydroxide, extracted with ether (4 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a tacky oil: yield 0.104 g. This oil was combined with picric acid (0.110 g) and ethanol (1.0 ml) and heated into solution. Upon standing for 2 days at room temperature, a bright yellow solid had formed which was recrystallized from methanol: yield 0.037 g (9%); mp 167-169° (lit. 103 171-173°). The hydrochloride salt was prepared by dissolving 6,7-benzomorphan in ether and making acidic with hydrogen chloride gas. Recrystallization from ethanol/ether gave beautifully developed white crystals: mp 250-253°; nmr (D₂O) δ 1.80-4.31 (broad methylene-methine envelope, 10) 7.34 (s, 4, aromatic protons).

2-Methyl-8-oxo-6,7-benzomorphan (72). 108 --2-Methyl-6,7-benzomorphan hydrochloride (5.22 g, 0.024 mol) was dissolved in water (10 ml), made basic with 10 percent sodium hydroxide, extracted with ether (4 x 25 ml), and dried (magnesium sulfate). The ether was removed under vacuum and the resultant clear oil dissolved in acetic anhydride (26 ml), placed in an ice-salt-water bath, and stirred until cold. To the cold solution was added concentrated sulfuric acid (3.3 ml) all at once and chromium trioxide (6.6 g) in acetic anhydride (28 ml) over a 2 hr period. (Note: the chromium trioxide was added to cold acetic anhydride to prevent a possible explosion). The resultant solu-
tion was allowed to stir in the ice-salt-water bath an addition 3 hrs, dumped into chipped ice (about 200 g), made basic with 10 percent sodium hydroxide, extracted with ether (10 x 100 ml), and dried (magnesium sulfate). The ether was removed under vacuum and the resultant yellow-brown oil was combined with a saturated solution of picric acid in acetone (5 ml). The resulting picrate was removed via filtration and washed with cold acetone and hot absolute ethanol: mp 194-195.5° (lit. 194°). The free amine was regenerated by chromatographing the picrate over alumina (60 g, 26 x 2 cm) (Woelm neutral): yield 3.46 g (72%); ir, cm⁻¹ (neat) 1676 (C=O) 1601 (aromatic); nmr (CDCl₃) δ 2.37 (s, 3, CH₃) 1.44-3.48 (broad methylene-methine envelope, 8) 7.44 (m, 3, aromatic protons) 8.07 (m, 1, aromatic proton).

2-Methyl-8β-hydroxy-6,7-benzomorph (81b).—Method A: A mixture of 2-methyl-8-oxo-6,7-benzomorph (0.071 g, 0.35 mmol), ethanol (25 ml), concentrated hydrochloric acid (0.2 ml), and platinum oxide (0.020 g) was placed in a Parr Hydrogenator for 24 hrs at an initial pressure of 50 pounds per square inch and ambient temperature. The hydrogen uptake was 1.6 pounds per square inch. The catalyst was removed via filtration and the solvent was removed under vacuum leaving a tacky residue. This residue was dissolved in water (10 ml), made basic with 10 percent sodium hydroxide, extracted with ether (4 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a clear oil: ir, cm⁻¹ (neat) 3650 (OH); nmr (CDCl₃) δ 0.96-3.30 (broad methylene-methine envelope, 8) 2.70 (s, 3, CH₃)
3.98 (s, 1, OH-washes out with D₂O) 4.76 (d, 1, H, J₃H₋₇H = 6.5 Hz) 7.13 (m, 3, aromatic protons) 7.64 (m, 1, aromatic proton). The oil was dissolved in ether and the solution made acidic with hydrogen chloride gas. The resultant hydrochloride was recrystallized from ethanol/ether: yield 0.019 g (22.9%); mp 218-221°.

Method B: With ice cooling a solution of sodium borohydride (0.450 g, 12 mmol) in water (9 ml) and methanol (36 ml) was added to a stirred solution of 2-methyl-8-oxo-6,7-benzomorphan (0.474, 2.3 mmol) in methanol (30 ml). The reaction mixture was gradually allowed to come to room temperature and stir for 24 hrs. The solution was made basic with 1 normal sodium hydroxide (20 ml), the solvent was removed under vacuum, and water (20 ml) was added. The aqueous solution was extracted with chloroform (6 x 25 ml) and dried (magnesium sulfate). The solvent was removed under vacuum leaving a tacky oil which was dissolved in ether and made acidic with hydrogen chloride gas. The resultant hydrochloride salt was recrystallized from ethanol/ether: yield 0.315 g (56.2%); mp 219-220°.

Method C: To a stirred solution of 2-methyl-8-oxo-6,7-benzomorphan (0.215 g, 1.1 mmol) in anhydrous ether (5 ml) was added a 1 molar solution of lithium aluminum hydride in ether (1.5 ml). After stirring an additional 1/2 hr, water (0.75 ml) was carefully added and the organic layer separated and dried (magnesium sulfate). The solvent was removed under vacuum and the residue dissolved in ether (5 ml). Hydrogen chloride gas was bubbled
through the ethereal solution and the resultant hydrochloride salt recrystallized from ethanol/ether: yield 0.074 g (29%); mp 218-220°.

Method D: \textsuperscript{113} (attempted). To a solution of 2-methyl-8-oxo-6,7-benzo-romoran (0.116 g, 0.58 mmol) in propanol (3.5 ml), sodium (0.180 g) was added over a 20 min period with the application of enough heat to maintain gentle reflux. After an additional 20 min of refluxing, the cooled solution was diluted with water (10 ml) and benzene (10 ml). The benzene layer was washed with a saturated solution of sodium chloride (2 x 10 ml) and dried (magnesium sulfate). The solvent was removed under vacuum leaving a tacky oil: VPC showed 6 significant peaks and no attempt was made to isolate or characterize any reaction product.

\textbf{Attempted preparation of 2-methyl-8α-hydroxy-6,7-benzo-morphan (81a).} \textsuperscript{111} --To a stirred solution of 2-methyl-8-oxo-6,7-benzo-morphan (0.337 g, 1.7 mmol) in 1 normal sulfuric acid cooled on an ice bath was added a solution of chromium trioxide (0.120 g) in 10 normal sulfuric acid (7 ml) over a 6 hr period. The solution was stirred an additional 1 hr at ice bath temperature and refrigerated overnight. The excess oxidant was destroyed with sodium bisulfite (0.30 g), and the pH was adjusted to pH 4 with sodium carbonate and to pH 11 with ammonium hydroxide. The cloudy solution was extracted with chloroform (5 x 50 ml) and dried (magnesium sulfate). The solvent was removed under vacuum leaving only unreacted starting material.
8-Oxo-6,7-benzomorphan (87). Method A: 119 2-Methyl-8-oxo-6,7-benzomorphan N-oxide (85). 105, 120 To a solution of 2-methyl-8-oxo-6,7-benzomorphan (0.166 g, 0.8 mmol) in methanol (5 ml) was added 30 percent hydrogen peroxide (0.1 ml) followed after 2 and 5 hrs by additional 30 percent hydrogen peroxide (0.1 ml). After 36 hrs at room temperature, the solution was concentrated under vacuum to about 2 ml, water (10 ml) was added, and the solvent removed under vacuum leaving a clear oil. This oil was made basic with hot aqueous sodium carbonate, extracted with chloroform (3 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum yielding a yellow oil which solidified upon standing: yield 0.150 g (83.1%); mp 158-161.5°.

2-Acetyl-8-oxo-6,7-benzomorphan (86). 119 A solution of 2-acetyl-8-oxo-6,7-benzomorphan N-oxide (0.56 g, 2.6 mmol) in acetic anhydride (0.92 ml) was stirred on a water bath with the temperature maintained at 50-60° for 1 1/2 hrs. To the cooled solution water (15 ml) was carefully added. The solution was concentrated under vacuum, basified with sodium carbonate, extracted with chloroform (3 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a tacky brown oil: yield 0.46 g; ir, cm⁻¹ (neat) 1676 (ketone C=O) 1650 (amide C=O).

8-oxo-6,7-benzomorphan (87). 119 A solution of crude 2-acetyl-8-oxo-6,7-benzomorphan (0.46 g) and 20 percent sulfuric acid (20 ml) was refluxed for 4 hrs, cooled, diluted with water, basified with sodium carbonate, extracted with chloroform (4 x 25 ml), dried (magnesium sulfate), and decolorized (charcoal).
The solvent was removed under vacuum, and the resultant black tacky residue was shown to be separable into 3 components on a thin layer system using Silica Gel GF$\text{254}$ as the adsorbent, acetone as the solvent, and iodine as the developer. This dark oil was chromatographed on a dry-packed$^{149}$ Silica Gel G column (0.05-0.20 mesh) (115 g) eluting with acetone and collecting 15 ml fractions. The initial material was a dark brown, unidentifiable substance: yield 0.121 g. The second compound was a yellow oil identical with 2-methyl-8-oxo-6,7-benzomorphan: yield 0.069 g. The third compound was an orange oil identical with 8-oxo-6,7-benzomorphan: yield 0.023 g. (4.3% based on recovered starting material).

Method B: A solution of 2-methyl-8-oxo-6,7-benzomorphan (0.171 g, 0.85 mmol) in water (5 ml) and 1 molar sulfuric acid (a few drops) was adjusted to pH 7 with sodium bicarbonate and placed on a water bath maintained at $30^\circ \pm 1^\circ$. To the stirred solution was added potassium permanganate (0.316 g) in water (10 ml) while maintaining the pH at 7 by adding 1 molar sulfuric acid. The slurry was maintained at $30^\circ \pm 1^\circ$ an additional hr, made acidic with 1 molar sulfuric acid, and filtered. The mother liquor was made alkaline with sodium carbonate, extracted with chloroform (4 x 25 ml), and dried (magnesium sulfate). The solvent was removed under vacuum yielding an orange-brown viscous oil: yield 0.039 g. A thin layer study using Silica Gel GF$\text{254}$ as the adsorbent, acetone as the solvent, and iodine as the developer showed a major unknown component plus 2-methyl-8-oxo-6,7-benzomor-
phan and 8-oxo-6,7-benzomorphan as minor components. No attempt was made to separate the 8-oxo-6,7-benzomorphan.

Method C: 122 (attempted). 2-Chloro-8-oxo-6,7-benzomorphan (88). A solution of 2-methyl-8-oxo-6,7-benzomorphan (0.171 g, 0.85 mmol) in toluene (4 ml) was added with stirring to a solution of 12.5 percent phosgene in benzene (1 ml) and toluene (4 ml) maintained at 10°. The temperature was allowed to gradually rise to room temperature, and the stirring was continued for 48 hrs. A white solid, which was identified as 2-methyl-8-oxo-6,7-benzomorphan hydrochloride, was removed via filtration: yield 0.081 g; mp 200-202°. The mother liquor was concentrated under vacuum yielding a red oil which was identified as crude 2-chlorocarbonyl-8-oxo-6,7-benzomorphan: yield 0.079 g; ir, cm⁻¹ (neat) 1675 (ketone) 1755 (chlorocarbamate). 8-Oxo-6,7-benzomorphan (87). The crude chlorocarbonyl compound (0.076 g) and water (10 ml) were heated at 70° for 4 hrs, cooled, made basic with ammonium hydroxide, extracted with chloroform (4 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving only starting material. The oil was combined with water (10 ml), refluxed 24 hrs, and worked up as above yielding only starting material. The oil was combined with 5 percent sodium hydroxide, heated at 70° for 4 hrs on a water bath, and worked up as above yielding only starting material. Method D: 106 2-Cyano-8-oxo-6,7-benzomorphan (89). To a solution of 2-methyl-8-oxo-6,7-benzomorphan (1.07 g, 5 mmol) in chloroform (10 ml)
was added with stirring over a 20 min period a solution of cyanogen bromide (0.841 g, 8 mmol) in chloroform (5 ml). The resultant solution was refluxed for 2 1/2 hrs, cooled, extracted with 15 percent hydrochloric acid (4 x 20 ml), washed with water (2 x 25 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving an orange oil: yield 0.86 g; ir, cm⁻¹ (neat) 2250 (CN). 8-Oxo-6,7-benzomorphan (87). This cyano intermediate was dissolved in 6 percent hydrochloric acid (15 ml), refluxed for 12 hrs, cooled, basified with concentrated ammonium hydroxide, extracted with chloroform (4 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a brown oily residue which showed two major peaks in the VPC: yield 0.695 g. Two compounds could be distinguished via a thin layer study using Silica Gel GF₂₅₄ as the adsorbent, acetone as the solvent, and iodine as the developer. The reaction mixture (0.695 g) was chromatographed on a dry-packed¹⁴⁷ Silica Gel G column (110 g) eluting with acetone and collecting 15 ml fractions on a fraction collector. The front running yellow fraction was identical with 2-methyl-8-oxo-6,7-benzomorphan: yield 0.31 g. The second, orange fraction was identified as 8-oxo-6,7-benzomorphan plus a minor impurity (VPC ratio about 30:1): yield 0.36 g (51% based on recovered starting material); ir, cm⁻¹ (neat) 3300 (NH) 1676 (C=0) 1600 (aromatic); nmr (CDCl₃) δ 1.44-3.64 (m, 8, methylene-methine envelope) 2.58 (s, 1, N-H-exchanges with D₂O) 7.42 (m, 3, aromatic protons) 8.11 (m, 1, aromatic proton).
**8β-Hydroxy-6,7-benzomorphan (41b).** —With ice cooling a solution of sodium borohydride (0.200 g, 5.3 mmol) in methanol (17 ml) and water (4 ml) was added to a solution of 8-oxo-6,7-benzomorphan (0.196 g, 1 mmol) (contained the impurity which could not be removed) in methanol (15 ml). The solution was allowed to come to room temperature and was stirred an additional 12 hrs. To the solution was added 1 normal sodium hydroxide (10 ml) and the solution was concentrated under vacuum. Water (10 ml) was added, the solution extracted with chloroform (5 x 15 ml), and dried (magnesium sulfate). The solvent was removed under vacuum, and the resultant oil, which could not be crystallized, still contained the impurity as shown via VPC. The oil was dissolved in ether, made acidic with a saturated solution of hydrochloric acid/ether, and the resultant hydrochloride recrystallized 3 times from acetone (2)/methanol (1)/ether: yield 0.035 g (14.8%); mp 278.5-282°.

**2-Acetyl-8-oxo-6,7-benzomorphan (90).** —To a solution of 8-oxo-6,7-benzomorphan (0.050 g, 0.27 mmol) in pyridine (2 ml) was added 3,5-dinitrobenzoyl chloride (0.250 g) in benzene (2 ml). After allowing this solution to stand overnight at room temperature, water (10 ml) and benzene (15 ml) were added, and the solution was made basic with sodium bicarbonate. The organic phase was separated, washed with water (2 x 25 ml), washed with 3 percent hydrochloric acid (3 x 25 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a solid residue which was recrystallized from
ethanol/chloroform: yield 0.010 g (8.8%); mp 217–219°C; ir, cm⁻¹ (KBr) 1676 (ketone) 1630 (amide C=O).

2-Tosyl-8-oxo-6,7-benzomorphan (91). —A solution of 8-oxo-6,7-benzomorphan (1.48 g, 8 mmol) (contained the impurity which could not be removed) in water (100 ml) was effected by making the mixture acidic with hydrochloric acid and then adjusting the pH to 7 with sodium carbonate. To this solution was added sodium carbonate (2.24 g) and p-toluenesulfonyl chloride (2.0 g, 10.5 mmol), and the resulting mixture was stirred on a water bath maintained at 80°C for 30 min then at room temperature for 12 hrs. The solid was removed via filtration, dried in a vacuum oven over phosphorous pentoxide, and recrystallized from methanol giving light brown needle crystals: yield first crop 1.36 g; mp 159.5–160.5°C; second crop 0.33 g; mp 157.5–159°C (overall 63.3%); VPC showed a single component; ir, cm⁻¹ (KBr) 1684 (C=O) 1599 (aromatic) 1160 (SO₂).

2-Tosyl-8β-hydroxy-6,7-benzomorphan (92b). —Method A: Sodium borohydride (0.100 g, 2.6 mmol) was added portionwise to a suspension of 2-tosyl-8-oxo-6,7-benzomorphan (0.836 g, 2.5 mmol) in 95 percent ethanol (5 ml). The stirred mixture was warmed to 50°C on a water bath for 30 min, allowed to stir 12 hrs at room temperature, and poured into crushed ice (about 20 g). The mixture was made acidic with hydrochloric acid, extracted with chloroform (4 x 20 ml), washed with 5 percent sodium carbonate, and dried
(magnesium sulfate). The solvent was removed under vacuum leaving a white solid which was recrystallized from benzene/petroleum ether (30-60°): yield 0.736 g (84%); mp 137.5-138.5°; ir, cm⁻¹ (KBr) 3512 (OH) 1595 (aromatic) 1160 (SO₂); nmr (CDCl₃) δ 2.43 (s, 3, CH₃) 4.86 (d, 1, Hₐ, Jₐₜₜ = 6.0 Hz) 1.34-4.58 (m, 9, broad methylene-methylene envelope + OH) 6.90-7.95 (m, 8, aromatic protons).

Anal. Calcd for C₁₉H₂₁O₃NS: C, 66.45; H, 6.16; N, 4.08; S, 9.34.

Found: C, 66.29; H, 6.21; N, 4.17; S, 9.14.

Method B: To a cooled solution of 2-tosyl-8-oxo-6,7-benzomorphanal (0.100 g, 0.3 mmol) in dry toluene (3 ml) was added aluminum isopropoxide (0.220 g). The solution was refluxed for 6 hrs, isopropyl alcohol (3 ml) was added, and the reaction flask was fitted with a partial reflux head and distilled. After 5 ml of liquid had been collected, the solution was cooled to room temperature, poured into saturated ammonium chloride in water, extracted with chloroform (4 x 100 ml), washed with a saturated solution of ammonium chloride (10 ml), washed with a saturated solution of sodium chloride (10 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a white solid which was recrystallized from benzene/petroleum ether (30-60°): yield 0.042 g (41.4%); mp 137-138.5°; VPC and TLC showed 1 compound.

8β-Hydroxy-6,7-benzomorphanal (41b). -- A mixture of 2-tosyl-8β-hydroxy-6,7-benzomorphanal (0.500 g, 1.5 mmol), lithium aluminum hydride
(0.370 g), and tetrahydrofuran (12 ml) was heated under reflux for 40 hrs, cooled, and decomposed by adding wet ether followed by water. The solid was removed via filtration and repeatedly washed with ether. The ether phase was separated and dried (magnesium sulfate). The solvent was concentrated under vacuum to about 20 ml and acidified with a saturated solution of hydrogen chloride/ether. The resultant hydrochloride was recrystallized from acetone (2)/methanol (1)/ether affording a well developed white crystalline product: yield 0.101 g (36.3%); mp 284-286° (dec). The free base could be regenerated: mp 114.5-115°; nmr (CDCl₃) (see Figure 5) δ1.19-3.45 (broad methylene-methine envelope, 8) 3.05 (s, 2, OH and NH-exchange with D₂O) 4.76 (d, 1, HA, JHAHC = 6.0 Hz) 7.18 (m, 3, aromatic protons) 7.65 (m, 1, aromatic proton).

Anal. Calcd for C₁₂H₁₆NOCl: C, 63.85; H, 7.14; N, 6.21; O, 7.09; Cl, 15.71. Found: C, 63.76; H, 7.20; N, 6.30.

Attempted epimerization of 2-tosyl-8β-hydroxy-6,7-benzomorphan. --

Method A: A solution of 2-tosyl-8β-hydroxy-6,7-benzomorphan (0.050 g, 0.15 mmol), 15 percent hydrochloric acid (0.5 ml), and acetone (3 ml) was refluxed for 12 hrs. Water (10 ml) was added to the cooled solution, the aqueous phase was extracted with chloroform (4 x 10 ml), washed with sodium carbonate (10 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving only unchanged 2-tosyl-8β-hydroxy-6,7-benzomorphan.

Method B: A solution of 2-tosyl-8β-hydroxy-6,7-benzomorphan (0.050 g,
0.15 mmol) in 0.5 normal potassium hydroxide in ethanol (5 ml) was heated at reflux for 5 hrs. Water (10 ml) was added to the cooled solution, the resultant mixture concentrated under vacuum, extracted with chloroform (4 x 10 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving only unchanged 2-tosyl-8β-hydroxy-6,7-benzomorphan.

2-Tosyl-8-chloro-6,7-benzomorphan (94).—A solution of 2-tosyl-8β-hydroxy-6,7-benzomorphan (0.100 g, 0.3 mmol) in thionyl chloride (0.1 ml) was placed in a flask equipped with a reflux condenser and a drying tube. The solution was allowed to stand at room temperature for 16 hrs, refluxed for 30 min, and decomposed with ice (10 g). The resultant mixture was extracted with chloroform (4 x 15 ml), washed with sodium carbonate (20 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving a viscous oil which solidified upon standing: yield 0.095 g; mp 130.5-132°; ir, no OH; VPC showed 2 major peaks.

Attempted preparation of 2-tosyl-8α-hydroxy-6,7-benzomorphan (92a).—

Method A: A mixture of crude 2-tosyl-8-chloro-6,7-benzomorphan (0.090 g) in 0.5 normal potassium hydroxide in ethanol (5 ml) was warmed to 50° with stirring to effect solution. The heating was continued for 3 hrs at which time water (10 ml) was added and the mixture concentrated under vacuum. The mixture was extracted with chloroform (4 x 10 ml), washed with water (15 ml),
and dried (magnesium sulfate). The solvent was removed under vacuum leaving only starting material.

Method B: A solution of the crude 2-tosyl-8-chloro-6,7-benzomorphan (0.095 g) in acetone (10 ml) was cooled to 0°. Water (0.1 ml) was added to the cooled solution followed by silver carbonate (0.082 g) in small portions over 15 min with shaking. The mixture was shaken an additional 30 min then warmed to 50-60° for 1 1/2 hrs. The mixture was filtered, the filtrate washed with acetone, and the combined acetone solutions dried (magnesium sulfate). The solvent was removed under vacuum leaving only starting material.

2-Tosyl-8β-tosyloxy-6,7-benzomorphan (95).—To a solution of 2-tosyl-8β-hydroxy-6,7-benzomorphan (0.300 g, 0.9 mmol) in pyridine (3 ml), p-toluenesulfonyl chloride (0.330 g, 1.7 mmol) was added. The solution was allowed to stand at room temperature for 48 hrs then poured into ice-water (60 ml) and stirred for 1 hr. The resultant white solid was removed via filtration and dried in a vacuum oven over phosphorous pentoxide: yield 0.410 g (94.3%); mp 136-140°; ir, cm⁻¹ (KBr) 1160 (N-SO₂) 1175 (O-SO₂) 1598 (aromatic); nmr (CDCl₃) δ 2.43 (s, 3, CH₃) 2.45 (s, 3, CH₃) 0.97-4.96 (broad methylene-methylene envelope, 8) 5.91 (d, 1, Hₐ, JₐHₐHₗ = 6.0 Hz) 7.02-8.16 (m, 12, aromatic protons).

2-Tosyl-8α-ethoxy-6,7-benzomorphan (96).—A solution of 2-tosyl-8β-tosyloxy-6,7-benzomorphan (0.300 g, 0.6 mmol) in 0.5 normal potassium hy-
droxide in ethanol (30 ml) was refluxed for 4 hrs. Water (60 ml) was added to the resultant cooled solution, and the resultant mixture was concentrated under vacuum, extracted with chloroform (4 x 25 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving an oil which was shown via VPC to be composed of two components. These components could be distinguished via TLC using Silica Gel GF$_{254}$ as the adsorbent, ether (2)/skellysolve (1) as the solvent, and iodine as the developer. The components were separated on a dry-packed silica gel G column (110 g) using ether (2)/skellysolve (1) as the solvent and collecting 5 ml fractions. The minor component was isolated as a white solid identical with 2-tosyl-8$_a$-hydroxy-6,7-benzomorphan: yield 0.031 g; mp 137.5-138.5°C. The major component was isolated as an oil and was identified as 2-tosyl-8$_a$-ethoxy-6,7-benzomorphan: yield 0.183 g; nmr (CDCl$_3$) $\delta$1.22 (t, 3, ethyl CH$_3$) 3.78 (q, 2, ethyl CH$_2$) 0.88-4.56 (broad methylene-methylene envelope, 8) 2.44 (s, 3, CH$_3$) 4.17 (d, 1, H$_B$, $J_{HBHC} = 0.6$ Hz) 6.98-7.94 (m, 8, aromatic protons).

2-Tosyl-8$_a$-hydroxy-6,7-benzomorphan (92a).—A mixture of 2-tosyl-8$_a$-tosyloxy-6,7-benzomorphan (0.704 g, 1.4 mmol) and water (1)/acetone (1) (350 ml) was heated to effect solution. The solution was refluxed for 6 hrs, cooled, concentrated under vacuum, extracted with chloroform (4 x 100 ml), washed with 5 percent sodium carbonate (200 ml), and dried (magnesium sulfate). The solvent was removed under vacuum leaving an oily residue which was crystallized by dissolving in benzene, adding petroleum ether (30-60°C) to
the cloud point, and seeding: yield 0.434 g (98.5%); mp 132.5-135.5°; nmr
(CDCl₃) δ 1.42-4.42 (broad methylene-methine envelope + OH, 9) 2.44 (s, 3,
CH₃) 4.51 (d, 1, H₄, J₃,₄ = 1.0 Hz) 7.00-7.92 (m, 8, aromatic protons).
The 2-tosyl-8α-hydroxy-6,7-benzomorphan was distinguishable from 2-tosyl-
8β-hydroxy-6,7-benzomorphan via TLC using Silica Gel GF₂₅₄ as the adsor-
bent, ether (2)/skellysolve C (1) as the solvent, and iodine as the developer.

8α-hydroxy-6,7-benzomorphan (41a). A reaction mixture of 2-
tosyl-8α-hydroxy-6,7-benzomorphan (0.517 g, 1.5 mmol), lithium aluminum
hydride (0.386 g), and tetrahydrofuran (12 ml) was heated at reflux for 40 hrs,
cooled, and decomposed with wet ether followed by water. The solid was re-
moved via filtration, the filtrate washed repeatedly with ether, and the com-
bined ether fractions dried (magnesium sulfate). The solvent was concen-
trated under vacuum and made acidic with hydrogen chloride/ether. The hydro-
chloride salt was recrystallized from acetone (2)/methanol (1)/ether: yield
0.108 g (32%); mp 218-220° (dec); nmr (D₂O) (see Figure 6) δ 1.45-4.03
(broad methylene-methine envelope, 8) 4.45 (d, 1, H₄, J₃,₄ = 1.0 Hz)
7.36 (m, 4, aromatic protons).

Anal. Calcd for C₁₂H₁₆NOCl: C, 63.85; H, 7.14; N, 6.21; O, 7.09;
Cl, 15.71. Found: C, 63.84; H, 7.24; N, 6.37.
Biological

Potentiation of the norepinephrine response by the stereoisomers of phenyl-2-piperidyl carbinol. —Male rats weighing 120-300 g were killed by a sharp blow on the head and both vas deferentia were removed and suspended in a water-jacketed (37.5°C) 10 ml tissue bath containing physiological salt solution of the following composition: NaCl, 136.8 mM; KCl, 2.68 mM, CaCl$_2$$\cdot$2H$_2$O, 1.36 mM; NaHCO$_3$, 11.9 mM; MgCl$_2$$\cdot$6H$_2$O, 0.49 mM; NaH$_2$PO$_4$, 0.36 mM; and glucose, 5.6 mM. The bath and stock solution were aerated with a mixture of oxygen (95%) and carbon dioxide (5%). Contractions were recorded on a smoked kymograph drum by an isotonic lever with a magnification of 1:20 exerting a tension of 350 mg. The lever was kept constantly vibrating at low frequencies by a small electric motor. Each tissue was washed five times during the first 10 min after being placed in the bath and allowed to equilibrate for 10 minutes after the last washing before any drugs were added.

Tissue was subjected to a single dose ($10^{-4}$ M) of norepinephrine. After the response had reached a maximum, the tissue was washed five times over a period of 5 min and then allowed to equilibrate for 10 min after the last washing. The second exposure to norepinephrine was taken as the control cumulative dose response curve. After this curve was obtained the tissue was washed as before and incubated with a dosage ($10^{-4}$ M) of a stereoisomer of phenyl-2-
piperidyl carbinol for 3 min, after which another cumulative dose response curve was determined for the norepinephrine in the presence of drug.

**Stereospecificity of catecholamine uptake by brain synaptosomes.**

Male Sprague-Dawley rats, 150-200 g, were sacrificed by cervical fracture, and the brains were quickly removed and dissected on a cold surface. Slices of cerebral cortex or striatum (caudate and putamen) were homogenized in 15 or 32 volumes of 0.25 M sucrose respectively, and centrifuged at 1,000 x g for 10 min in the cold. Aliquots of the carefully stirred supernatent fluid, equivalent to 6.7 mg of original cortex tissue (wet weight) and to 3.1 mg of striatum, were incubated for 5 min at 37°C in 2 ml of Krebs-Henseleit medium modified to contain one half the CaCl₂ concentration, ethylenediamine-tetraacetic acid (0.05 mg/ml), ascorbic acid (0.2 mg/ml), nialamide, a mono-amine oxidase inhibitor (1.25 x 10⁻⁵ M), ³H-(±)-norepinephrine (0.1 µM, 8.8 Ci/mmol, New England Nuclear Corp) a gas phase of 95% oxygen-5% carbon dioxide and 20 µl of solutions of test drugs in varying concentrations. The incubation was terminated by rapid chilling in an ethanol-ice water bath, after which each mixture was rapidly filtered in turn into 36 small gooch crucibles lined with millipore discs (Type B₆ nitrocellulose membrane filters, 20 mm diameter, 0.45 µ pore size) and mounted in 2 manifold vacuum assemblies. The filter discs were premoistened with 0.9% NaCl and after rapid filtration, 10 ml of ice-cold saline was used to wash out the incubation beakers and to rinse the filtered particles free of radioactive medium. After removal of most
of the moisture by filtration, the undersurfaces of the filter discs were carefully blotted free of excess moisture with filter paper, and the discs were placed in 10 ml of Bray's phosphor in a counting vial. Bray's phosphor completely dissolved the moist nitrocellulose membrane filters within 5-10 min. Tritium was then determined in a Packard Tricarb Model 3375 liquid scintillation spectrophotometer at 50% efficiency. In each experiment the radioactivity adhering to the membrane filters was estimated by filtering samples containing all the components of the incubation mixture except tissue. These blank values, comprising less than 10% of the tissue radioactivity, were subtracted from all tissue sample values. The tritium content of aliquots (0.1 ml) of the incubating medium was estimated after addition to 10 ml of Bray's phosphor. Tissue accumulation of radioactivity was expressed as tissue/medium ratio:

\[
\frac{\text{counts/min per gram of original tissue}}{\text{counts/min per ml of medium}}
\]

Tissue/medium ratios of tritium after incubating tissue for 5 min at 0° C were determined in a separate study using ice water in the metabolic shaker, and were subtracted from all 37° uptakes as diffusional blanks. These values were 0.7 ± 0.02 (6) for cortex, and 4.0 ± 0.2 (6) for striatum (means ± S. E. M., number of incubations in parentheses). Control tissue/medium ratios for the uptake of \(^3\text{H}-(-)\)-norepinephrine, 0.1 µM, at 37° were 3.2 ± 0.2 for cortex and 31.1 ± 1.3 (6) for striatum.
Coyle and Snyder\textsuperscript{78} reported that 85-95\% of the radioactivity taken up by synaptosomal preparations under these conditions of incubation was in the form of unmetabolized catecholamine. Consequently, tritium accumulation was taken as an indication of the uptake of $^3$H-(±)-norepinephrine. The time course of $^3$H-(±)-norepinephrine uptake in both brain areas was linear for 10 min.

$	ext{ID}_{50}$ values were determined as the concentration of drug inhibiting the 5 min uptake of $^3$H-(±)-norepinephrine by 50\%, after subtraction of 0\% tritium accumulation as a blank value. In a single $	ext{ID}_{50}$ determination 4 concentrations of each of a pair of enantiomorphs were added to incubation beakers in a constant volume of 20 μl. At each drug concentration, incubations were performed in quadruplicate. Percent inhibition of catecholamine uptake was plotted against the concentration of inhibitor on log probit paper, the resultant straight lines were connected by eye, and $	ext{ID}_{50}$ values were determined from the graph.

From 3 to 5 separate estimations of the $	ext{ID}_{50}$ were carried out for each isomer; thus each mean $	ext{ID}_{50}$ value reported in Tables 4, 5, and 6 represents a minimum of 60 separate incubations. Relative potency values were expressed as the relationship of the mean $	ext{ID}_{50}$ values for each compound to that of (−)-ephedrine in cortical synaptosomes ($7.2 \times 10^{-7}$):

$$\text{Relative potency} = \frac{7.2 \times 10^{-7}}{\text{ID}_{50} \text{ test drug}} \times 100$$

Statistical differences in relative potency between isomers were determined by Student's t test.
Lipolysis studies with the ephedrine isomers, the phenyl-2-piperidyl carbinol isomers, and the 8-hydroxy-6,7-benzomorphan diastereomers.— The method of Finger and co-workers\textsuperscript{137} was used. Nonfasted, white, male Harlan-Wistar rats weighing 225 ± 50 g were employed in this study. Animals were sacrificed by a sharp blow on the head and the anterior one-third of the epididymal fat pad was transferred to Krebs-Ringer bicarbonate buffer (pH 7.4) which was prepared by combining 20 ml of 4.5% NaCl solution, 0.8 ml of 5.75% KCl solution, 0.6 ml of 8.1% CaCl\cdot H_{2}O solution, 0.2 ml of 12.2% KH\textsubscript{2}PO\textsubscript{4}\cdot H_{2}O solution, and 0.2 ml of 19.1% MgSO\textsubscript{4}\cdot 7H_{2}O solution with 87.2 ml of water. To the above solution was added 21 ml of 1.3% NaHCO\textsubscript{3} and the resultant solution was aerated for 10 min with oxygen (95%)–carbon dioxide (5%). After the pooling of fat pads from at least 3 rats for each experiment, the tissue was minced to yield pieces weighing about 5–15 mg. For each test 300 mg of adipose tissue fragments were added to 2.5 ml of the buffer solution containing 4% albumin as an acceptor for the released free-fatty acids. Any antagonists (inhibitors) were added in 0.1 ml volumes, such that the overall drug concentration would be 10\textsuperscript{-3}, 3.16 \times 10\textsuperscript{-4}, 10\textsuperscript{-4}, 3.16 \times 10\textsuperscript{-5}, or 10\textsuperscript{-5} M, and the experiments were preincubated at 37\textdegree C in an atmosphere of oxygen (95%)–carbon dioxide (5%) for 15 min. The agonist, either the drug to be tested or norepinephrine, was next added in a 0.1 ml volume so that the 0.1 ml would deliver enough drug to yield a 10\textsuperscript{-3}, 10\textsuperscript{-4}, or 10\textsuperscript{-5} M solution or enough norepinephrine to yield a 10\textsuperscript{-4} M solution. After incubating for 60 min at 37\textdegree C in
an atmosphere of oxygen (95%)-carbon dioxide (5%), the reaction was stopped by adding 2.5 ml of 10% trichloroacetic acid. In order to monitor the results, a buffer blank, a glycerol standard, a norepinephrine standard, a control lacking only drug which was stopped before incubation ($t_0$), and a control lacking only drug which was stopped after incubation ($t_{60}$) were included in each experimental run. Duplicate 2.0 ml suspensions of the incubation media were centrifuged and 1.0 ml aliquots of the supernatant used for glycerol assay.

The glycerol assay was conducted as follows: To 1.0 ml of the above supernatant, 0.05 M sodium metaperiodate (0.3 ml) was added to oxidize the glycerol to formaldehyde + formic acid. The solutions were mixed on a vortex and allowed to stand for 10 min. Next, 0.5 M sodium arsenite (0.3 ml) was added to destroy the excess periodate. The solutions were mixed on a vortex and allowed to stand for 10 min. A solution of 0.4% 2,4-pentane-dione in 4 M ammonium acetate buffered to pH 6.5 with acetic acid (1.5 ml) was added to form a colored product with formaldehyde. The solutions were mixed on a vortex, incubated in a water bath at 60° for 10 min, and cooled. The optical density was then determined spectrophotometrically at a wavelength of 412 mp.

The agonist activity was determined by subtracting the optical density value of the $t_{60}$ control from the optical density value of the samples. In all cases the resultant values were about zero implying no agonist activity. The antagonist activity was determined by subtracting the $t_{60}$ control value from
the norepinephrine standard value and the sample values and using these corrected values to calculate the percent inhibition at each concentration according to the following equation:

$$\% \text{ inhibition} = 100 - \frac{\text{corrected sample value}}{\text{corrected norepinephrine standard value}}$$

From 3 to 5 experiments were conducted at each concentration and the mean % inhibition value ± S. E. M. were plotted against -log M. The points were connected by eye and the ID$_{50}$ values were determined from these graphs. The relative potency of each compound was also calculated by comparing the ID$_{50}$ values of each compound to the ID$_{50}$ value of the most potent compound, 1R, 2S-(−)-ephedrine (1.3 × 10$^{-5}$ M) as follows:

$$\text{Relative potency} = \frac{1.3 \times 10^{-5}}{\text{ID}_{50} \text{ of test compound}} \times 100$$
SUMMARY

In an attempt to extend existing knowledge of the stereochemical requirements of the adrenergic receptor, the stereoisomers of phenyl-2-piperidyl carbinol were prepared. This compound is chemically related to the known adrenergic agents ephedrine, methylphenidate, and pipradrol. The previously assigned erythro and threo configuration was confirmed by an NMR study utilizing the vicinal coupling constants of the benzylic protons. The absolute configuration of the four stereoisomers was assigned on the basis of a circular dichroism correlation with the ephedrine stereoisomers of known configuration.

In order to study the conformational requirements of the adrenergic receptor, the diastereomeric 8-hydroxy-6,7-benzomorphanes were prepared. These compounds are rigid phenethylamine analogs resembling phenyl-2-piperidyl carbinol in their chemical make-up. The relative configuration of these diastereomers was assigned on the basis of the vicinal coupling constants of a benzylic proton.

The stereoisomers of phenyl-2-piperidyl carbinol were tested to determine their ability to potentiate the effect of norepinephrine on the rat vas deferens. It was found that all four stereoisomers potentiate the norepinephrine
effect to a small, though significant and nonstereoselective, extent.

The stereoisomers of phenyl-2-piperidyl carbinol, the stereoisomers of ephedrine, and the diastereoisomers of methylphenidate were tested to determine their effects on the inhibition of $^3$H-(±)-norepinephrine uptake by the noradrenergic and dopaminergic synaptosomes of the rat brain. The threo-phenyl-2-piperidyl carbinols were found to be more effective than the erythro-phenyl-2-piperidyl carbinols as inhibitors in both the noradrenergic and dopaminergic fractions, and a stereoselective inhibition was found in the dopaminergic receptors with the 1R, 2R-(−)-phenyl-2-piperidyl carbinol being the most potent inhibitor. Likewise, the threo-methylphenidate was found to be a more effective inhibitor than the erythro-methylphenidate on both the noradrenergic and dopaminergic synaptosomes. A different stereoselectivity pattern was observed for the ephedrine isomers with the 1R, 2S-(−)-isomer being the most potent inhibitor in both the noradrenergic and dopaminergic fractions.

The effects of the stereoisomers of phenyl-2-piperidyl carbinol, the diastereomers of 8-hydroxy-6,7-benzomorphan, and the stereoisomers of ephedrine on lipolysis were determined. It was found that all compounds lacked agonist activity. However, a consistent pattern emerged in the evaluation of these compounds as antagonists of norepinephrine induced lipolysis. All compounds inhibited this induced lipolysis and this inhibition was stereo-
selective in favor of the 1R, 2S-configuration and the conformation assumed by 8β-hydroxy-6,7-benzomorphan.


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100. (a) R. Grewe, Naturwissenschaften, 33, 333 (1946); (b) R. Grewe, Angew. Chem., 59, 194 (1947); (c) R. Grewe and A. Mondon, Ber. Chem. Ges., 81, 279 (1948).


119. M. Polonovski and M. Polonovski, Compt. rend., 184, 331 (1927).


135. C. K. Buckner, personal communication.


141. D. R. Feller and O. S. Lee, personal communication.


147. B. Loev and M. M. Goodman, Chem. and Ind., 2026 (1967).