Synthesis of 2-*exo*- and 2-*endo*-Mecamylamine Analogues. Structure–Activity Relationships for Nicotinic Antagonism in the Central Nervous System

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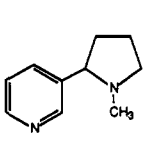
Nine analogues of mecamylamine (**2**) which differ in the number and substitution pattern of methyl groups, were prepared. In four of these analogues the amine functionality is in an endo orientation. Enantiomers of 2-*endo*- and 2-*exo*-*N*-methylfenchylamine (**25** and **26**, respectively) were also prepared. The hydrochloride salts of these compounds were tested for nicotinic antagonism relative to mecamylamine in vivo and none was found to be as potent as mecamylamine, although a broad range of activity was observed. In general, methyl substituents at the C1, C2, and C7 positions of the mecamylamine structure do not appear to be significant for antagonistic activity. Methyl substituents at C3, however, appear to be very important for activity. Three sets of enantiomers of *N*-methylfenchylamine analogues, **28–30**, possessing structural features of mecamylamine and nicotine were also prepared. These compounds were inactive as antagonists. Only a small degree of stereoselectivity was elicited in this series, less than that seen with enantiomers of nicotine. Antagonists with the exo *N*-methylamine functionality are slightly more active than the endo isomers. The extent to which structural modification might change lipophilicities was estimated through calculated partition coefficients; such changes alone appeared insufficient to explain differences in activities of the analogues. Lastly, a tolerance for a tertiary (dimethyl) amine functionality was demonstrated in addition to the lack of tolerance for bulkier substituents at C3 or on the nitrogen.

Initial evidence for the existence of central nicotinic acetylcholine receptors was based upon the fact that the behavioral effects of nicotine (**1**) were antagonized by ganglionic blockers that penetrate the central nervous system (CNS), e.g., mecamylamine (**2**) and pempidine (**3**).



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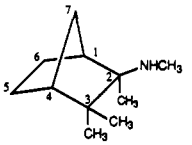

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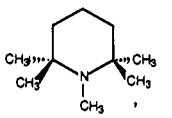

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For example, nicotine has been shown to produce depression of spontaneous activity in a number of species.[1,2] Both acute and chronic effects of nicotine on this locomotor activity are dose-dependent and are selectively antagonized by mecamylamine, but not by hexamethonium. Nicotine has also been shown to produce centrally mediated antinociception, and mecamylamine and pempidine, unlike hexamethonium or other quaternary ganglionic blockers,[3,4] selectively antagonize this effect.[5]

Since nicotine-induced alterations of locomotor activity and antinociception are selectively antagonized by central nicotinic antagonists, it is possible that antagonism involves a direct interaction of the antagonists with nicotinic receptors. A limited amount of evidence suggests, however, that mecamylamine and pempidine are noncompetitive antagonists in the CNS. For example, these compounds have not been shown to displace bound [^{3}H]nicotine or [^{3}H]acetylcholine in brain tissue in vitro.[2,6] Mecamylamine also antagonizes the nicotine cue in rats in a noncompetitive manner. This antagonism could not be overcome by increasing the dose of nicotine.[7] However, no pharmacological studies involving nicotine's behavioral effects have been conducted to support the noncompetitive nature of nicotinic antagonism in the CNS.

If central nicotine antagonists are noncompetitive, then their effects may be mediated through a receptor site that is different from the nicotine receptor. Alternatively, central nicotine antagonists may exert their effects noncompetitively by some nonreceptor-mediated mechanism, e.g., direct blockage of ion channels. Pharmacological criteria for a receptor-mediated mechanism of action includes structure–activity relationships. The structural requirements for antagonism of the central effects of nicotine, however, have yet to be thoroughly documented.

On the basis of present literature, central antagonists of nicotine do not appear to have stringent structural requirements.[8-11] This is not supportive of the idea that central nicotine antagonist may act at the nicotinic receptor site. Various reports, however, have demonstrated the general importance of aliphatic substitution about the secondary or tertiary amine functionality.[8] This may or may not be related to the aliphatic substitution pattern about the pyrrolidine nitrogen of nicotine. To further elucidate any possible structural requirements, we tested a series of analogues of mecamylamine for blockade of nicotine's depression of spontaneous activity and its antinociceptive effect. Mecamylamine was chosen for these studies because its rigid structure provides a suitable template for synthesis of receptor probes. In particular, we were interested in how changing the orientation of methyl substituents on the bicyclic ring would affect biological activity. Any observable structure–activity rela-

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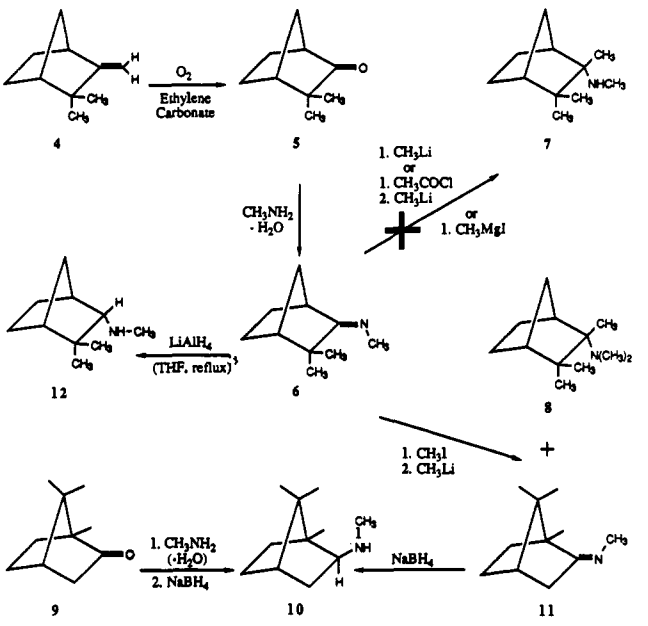
Scheme I



tionships in this regard would be supportive of receptor-mediated antagonism.

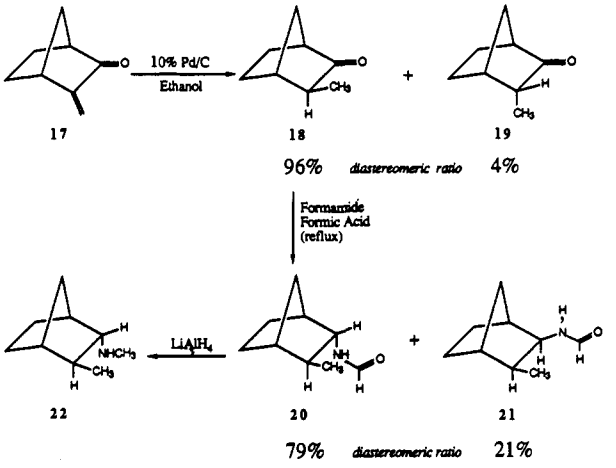
Chemistry

Optical resolution of racemic mecamylamine (**2a**) was carried out through the preparation of (*R*)-(−)- and (*S*)-(+)-10-camphorsulfonate salts, which were purified by recrystallization using acetone as a solvent, an adaptation of the procedure of Stone et al.[8]

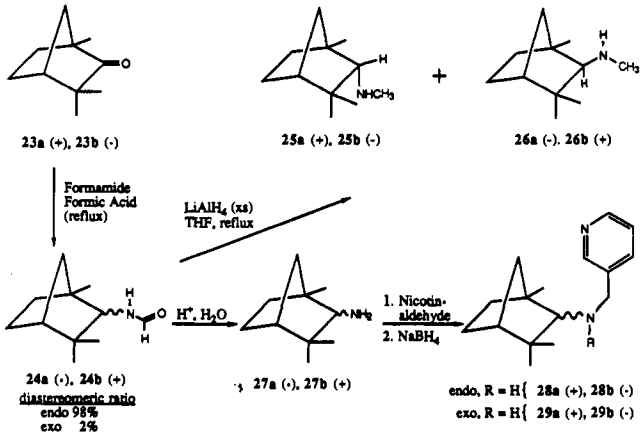
Initially, camphenilone (**5**) (recently discontinued) was purchased from the K & K Laboratories. An alternate supply of **5** was prepared in our laboratory by bubbling oxygen through a solution of camphene (**4**) in ethylene carbonate at 140 °C for 28 h in about 16% yield with recovery of starting material (Scheme I).[12] Several attempts at preparing **5** and **4** using chromium trioxide in glacial acetic acid essentially by the procedure of Zeiss and Zwanzig for 1-methyl-α-fenchene were unsuccessful.[13]

Camphenilone (**5**) was treated with methylamine to give the Schiff's base, camphenilimine **6** in good yields (Scheme I). Treatment of **6** with methyllithium, or methyl magnesium iodide, in refluxing tetrahydrofuran (THF) failed to give *endo*-mecamylamine (**7**) presumably due to the great amount of steric hindrance around the C2 position. Formation of the *N*-acyliminium ion followed by treatment with methyllithium was also unsuccessful.[14] Formation of the *N,N*-dimethyliminium salt, however, followed by treatment with methyllithium gave minor amounts of *N*-methylmecamylamine (**8**) as evidenced by GC/MS. Compound **8** is presumed to be the endo isomer as the top face of the iminium salt is less sterically hindered than the lower face. The major product of the above reaction, after reduction with sodium borohydride, was *N*-methylisobornylamine (**10**) as revealed by spectral comparisons to a sample of **10** prepared independently from **9**. These data, in addition to mass spectral analysis, showed this major product to be the rearranged *N*-methylimine of camphor **11**. The difficulty of adding nucleophiles to the imine functionality in this bicyclic system was further demonstrated in that **6** was reduced with lithium aluminum hydride ($LiAlH_4$), in refluxing THF, to give *endo*-2-demethylmecamylamine (**12**) in only 24% yield with significant recovery of starting material.

Scheme II



Scheme III



The *N*-methyl tertiary amine derivative of mecamylamine 13 (Table I) was obtained in low yields (35%) by treating mecamylamine with iodomethane followed by treatment with sodium methoxide. The *N*-methyl derivatives of *exo*- and *endo*-2-aminonorbornane (**14** and **15**, respectively) were prepared in moderate yields (~60%) by the reduction of the carbamate formed from 2-aminonorbornane and 4-nitrophenyl chloroformate. The tertiary *N,N*-dimethylisobornylamine (**16**) was also prepared by treatment of **10** with formic acid and formaldehyde in 12% yield.

For the preparation of a 2,3-didemethyl analogue of mecamylamine with which the importance of the C3 *gem*-dimethyl substituent could be evaluated, 3-methylenenorbornan-2-one (**17**) was hydrogenated with use of Pd/C to give *exo*- and *endo*-3-methyl-norbornan-2-one (**18** and **19**, respectively) in a diastereomeric ratio of 96:4 as determined by GC/MS analysis (Scheme II). The predominant exo isomer **18** was purified by column chromatography and converted to the endo **20** and exo **21** C2 *N*-formyl derivatives in a diastereomeric ratio of 79:21, respectively, also as determined by GC/MS analysis.[15] The predominant endo isomer **20** was reduced with $LiAlH_4$ to give a racemic mixture of *exo*-3-methyl-*endo*-*N*-methylnorborn-2-ylamine (**22**) as confirmed by X-ray crystallog-

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(13) Zeiss, H. H.; Zwanzig, F. R. *J. Am. Chem. Soc.* **1957**, *79*, 1733.
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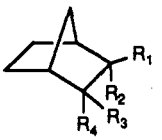
Table I. Relative Potency of Bicyclic Mecamylamine Analogues with Substituents at C(2) and C(3)

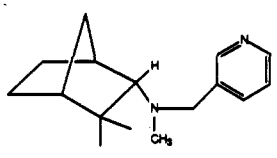


compd	+/−	R_1	R_2	R_3	R_4	relative potency[a]	log P_{calc}[b]
2a	±	$NHCH_3$	CH_3	CH_3	CH_3	1.0	3.53
2b	−	$NHCH_3$	CH_3	CH_3	CH_3	1.4	3.53
2c	+	$NHCH_3$	CH_3	CH_3	CH_3	3.0[c]	3.53
12	±	H	$NHCH_3$	CH_3	CH_3	1.2	3.01
13	±	$N(CH_3)_2$	CH_3	CH_3	CH_3	1.5	3.96
14	±	$NHCH_3$	H	H	H	>40[d]	1.97
15	±	H	$NHCH_3$	H	H	>40[e]	1.97
22	±	H	$NHCH_3$	CH_3	H	18.1	2.49
31	±	$NHCH_2CH_3$	H	phenyl	H	stimulant	4.15

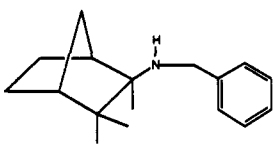
[a] Potency relative to racemic mecamylamine (**2a**). [b] As calculated by Rekker et al.[17] [c] AD_{50} could not be determined for spontaneous activity. [d,e] Maximum antagonism at 10 mg/kg: 5% and 21%, respectively.

raphy and spectral analyses. An overall yield of 28% was obtained.

Optically active analogues of mecamylamine lacking a methyl group at the C2 position and possessing a methyl group at the bridgehead carbon were prepared by using optically active fenchone as starting material (Scheme III). The (+) and (−) enantiomers of fenchone, **23a** and **23b**, respectively, were each treated with formamide and formic acid under reflux conditions to give predominantly the *endo-N*-formylfenchylamines (**24a** and **24b**, respectively) along with minor amounts of the exo isomers as indicated by GC/MS analyses, which showed a diastereomeric ratio of 98:2 (endo to exo).[15] Diastereomeric assignments were based upon the expected course of the Leukhart reaction. Compounds **24a** and **24b** were reduced with $LiAlH_4$ to give predominantly the enantiomers of *endo-N*-methylfenchylamine **25a** and **25b**, respectively, which were obtained in overall yields of about 55%. Also isolated were lesser quantities of the exo isomers, **26a** and **26b**. Stereoisomers possessing structural features of both nicotine (**1**) and mecamylamine (**2**) were also prepared from **24** by way of acid hydrolysis to the fenchylamine intermediates **27a** and **27b** (Scheme III). These enantiomers were each condensed with nicotinaldehyde and reduced to give the endo enantiomers of *N*-(3-methylenepyridyl)fenchylamine (**28a** and **28b**). Minor amounts of the exo enantiomers **29a** and **29b** were also obtained and characterized. The *N*-methyl derivatives **30a** and **30b** of the endo isomers were also prepared. Spectral and analytical data confirmed the



30a (+), 30b (·)



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structures of these analogues. The HCl and 10-camphorsulfonate salts of these analogs were prepared for crystallization and X-ray studies. All crystals obtained, however, were unsuitably "twinned" and diastereomeric assignments of these analogues could not be confirmed.

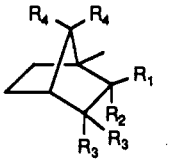
Pharmacological Results and Discussion

The relative potencies of all tested compounds compared to (±)-*exo*-mecamylamine (**2a**, Table I) were calculated from the following pharmacological data. Nicotine (**1**) produced depression of spontaneous activity and antinociception with ED_{84}'s of 1.71 and 2.56 mg/kg, respectively. Compound **2a** antagonized the effect of nicotine at these ED_{84} doses with AD_{50}'s of 0.24 (0.14–0.42) mg/kg for depression of spontaneous activity and 0.08 (0.02–0.29) mg/kg for antinociception. For depression of spontaneous activity, (−)-*exo*-mecamylamine (**2b**, Table I) was approximately equipotent with **2a**. For the (+) isomer **2c**, however, no antagonism was found at 3.0 mg/kg due to the fact that this dose produced 55% depression of spontaneous activity when given 10 min prior to saline. Therefore, an AD_{50} could not be calculated for this compound in this assay. However, both the (−) and (+) antipodes of *exo*-mecamylamine were found to have similar potency to the racemate **2a** for antagonism of nicotine-induced antinociception. The 2-demethyl derivative of (±)-*endo*-mecamylamine **12** possesses similar potency to **2a** for antagonism of nicotine-induced depression of spontaneous activity and antinociception. The N-methylated derivative of (±)-*exo*-mecamylamine **13** (Table I) is as potent as the parent compound for antagonism of depression of spontaneous activity and antinociception. None of these compounds, other than **2c**, elicited agonist effects in either assay.

The racemates of *exo*- and *endo-N*-methylnorborn-2-ylamine, **14** and **15**, respectively, were inactive up to 10 mg/kg in both assays. These data are in contrast to the antagonistic activity of *exo*-3-methyl-*endo-N*-methylnorborn-2-ylamine (**22**) which exhibited weak to moderate antagonistic activity. Racemic fencamphamine (**31**) was also tested for antagonistic activities in these assays.[16] This compound, however, appeared as a stimulant for spontaneous activity, and no antagonism of nicotine-induced antinociception was observed at a dose up to 10 mg/kg (Table I). *N*-Methylisobornylamine (**10**) as well as its *N*-methyl counterpart **16** were moderately effective in blocking both nicotine effects. No evidence of agonistic activity was seen for either of these compounds at the highest dose tested for antagonism. The (+)- and (−)-endo isomers of N-methylfenchylamine, **25a** and **25b**, respectively, were equally effective in blocking nicotine-induced depression of spontaneous activity. However, the (+)-endo isomer was approximately 4 times more potent than the corresponding (−) isomer in antagonizing nicotine-induced antinociception. On the other hand, their (−)- and (+)-exo counterparts, **26a** and **26b**, respectively, had similar potencies in both assays (Table II). Derivatives of fenchylamine, **28–30**, possessing an N-substituted pyridinyl functionality did not produce greater than 40% antagonism up to doses of 10 mg/kg. None of these compounds elicited agonistic activities in either assay up to 10 mg/kg.

(16) Obtained from Aldrich.

Table II. Relative Potency of Bicyclic Mecamylamine Analogues with Substituents at C(1), C(2), C(3), and C(4)



compd[b]	+/-	R_1	R_2	R_3	R_4	relative potency[a]	log P_{calc}[c]
10	±	$NHCH_3$	H	H	CH_3	8.6	3.53
16	±	$N(CH_3)_2$	H	H	CH_3	10.5	3.96
25a	+	H	$NHCH_3$	CH_3	H	1.9	3.53
25b	-	H	$NHCH_3$	CH_3	H	6.2	3.53
26a	-	$NHCH_3$	H	CH_3	H	1.7	3.53
26b[d]	+	$NHCH_3$	H	CH_3	H	1.2	3.53

[a] Potency relative to mecamylamine (2a). [b] **a** compounds synthesized from (+)-fenchone, **b** compounds, from (-)-fenchone. [c] As calculated by Rekker et al.[17] [d] Not optically pure.

Structure-Activity Relationships

Very little enantioselectivity was observed with optically active samples of **2a** and **26**. For mecamylamine, the (-) antipode **2b** was slightly more potent, and for **26**, the (+) isomer **26b** was slightly more potent (Tables I and II). Likewise, **25** showed some enantioselectivity; **25a** was 3.2 times more potent than **25b** (Table II).

A comparison of the activities of **2a** and **26** shows that a methyl group can be exchanged between the C1 and C2 positions without significantly affecting biological activity (Tables I and II). This suggests that C1 and C2 methyl groups are not directly involved in a receptor-mediated mode of action, or that if a receptor site exists, it is equally specific for both of these functionalities.

The difference in activities between analogues with a C1 or C2 methyl group and those without may be due, in part, to the C1 or C2 methyl group's effect on biodisposition. Removal of the C1 or C2 methyl group lowers the calculated partition coefficient from 3.53 to 3.01.[17] That **2a** and **12** are similar in their potencies, despite this change in lipophilicity, implies that the C2 methyl group may be somewhat beneficial to activity. The endo/exo nature of the amine functionality, however, must also be considered.

A comparison of the relative potencies of compounds **25** and **26** indicates that exo and endo isomers of mecamylamine analogues are nearly equipotent (Table II). An exception, however, is found with the exo isomer of the (-) antipode **25b** which was found to be 5.2 times more potent than the endo isomer of the (+) antipode **26b**. Both these compounds originated from (-)-fenchone (**23b**).

For the optimal activity of a mecamylamine analogue, the *gem*-dimethyl group should be located at C3, as in **26**, rather than at C7, as in **10**. A comparison of the activities of these two compounds shows that translocation of the *gem*-dimethyl group from C3 to C7 reduces potency by a factor of 5.6 (Table II). This is significant in that in the case of a C3 *gem*-dimethyl group, the *N*-methylamine functionality is less sterically hindered and more able to interact with any potential receptor site. A hydrophobic interaction between the C3 methyl group and a receptor site, however, is also conceivable.

Methyl groups on the norbornane ring system, including those at C7 and C1 are vital for biological activity. Removal of these groups from **10** gives **14**, which has almost no antagonistic properties (Table I). This illustrates the role that the methyl substituents may be playing in biodisposition. According to calculated partition coefficients, **10** should be about 36 times more lipophilic than **14**.[17]

A comparison of the activities of **22** with **15** shows that a methyl group at the C3 position is vital to activity. This may be due, in part, to the C3 methyl's effect on biodisposition; however, the relatively small change in P_{calc}, a factor of 3.3, along with the restoration of activity observed upon the addition of a C3 methyl to **15** clearly demonstrates that this group is required for antagonistic activity (Table I). Compound **22**, therefore, represents the minimal structure required for activity of a mecamylamine analogue.

Comparisons of the activities of **22**, **25**, and **10** demonstrate the importance of a C3 methyl group for biological activity. Compound **22** differs from **25** in that it lacks the C1 and endo C3 methyl groups. This makes **22** less lipophilic than **25** by a factor of 10, according to calculated partition coefficients. Compound **22**, however, is less potent than **25** only by a factor of 4.6 (Tables I and II). Comparing the activities of **22** and **10** shows that a single methyl group at the C3 position is almost as important for biological activity as are three methyl groups at the C7 and C1 positions. Compounds **22** and **10** are nearly equipotent yet the calculated partition coefficients of these compounds differ by a factor of 10.

Although a single methyl group at C3 appears to be vital for activity, adding a second methyl group to the C3 position on **22** gives **12**, which is 13 times more potent (Table I). The differences in the calculated partition coefficients and activities between **12** and **22** suggest that the log of an optimal calculated partition coefficient lies somewhere above 3.00. The calculated log *P* for pempidine (**3**), which is more potent than **2a** in some assays, is 3.29.

Stone et al. showed that *N*-demethyl-*N*-ethylmecamylamine had a relative potency of 1.7 and 1.2 as compared to mecamylamine in nicotine–convulsion and pupil–dilatation in vivo assays, respectively.[8] Therefore, the lack of antagonistic activity in fencamphamine, (**31**) can be attributed to the bulky phenyl substituent at C3, which may hinder any attachment to an antagonistic binding site and/or completely alter the pharmacology (Table I). The calculated partition coefficient of this compound, however, is only 35% greater than that of **13**, a very potent antagonist. This, in consideration with fencamphamine's structural similarities to other potent nicotinic antagonists, supports the idea that nicotine antagonists have particular structural requirements for activity.

Stone et al. also showed that bulky substituents on the nitrogen of mecamylamine analogues significantly dimin-

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ished biological activity.[8] For example, *N*-demethyl-*N*-benzylmecamylamine (**32**) was found to be 62 times less potent than mecamylamine (**2a**) in nicotine–convulsion assays, and 64 times less potent in pupil–dilatation assays. Similarly, we have found that both **29a** and **29b** are very weak antagonists. These results are of interest because of the structural similarities to nicotine (**1**). The lack of significant antagonist activity of **29** lends support for noncompetitive antagonism of nicotine by mecamylamine analogues, as it does not appear that the agonists and antagonists possess similar structural requirements for their activity.

In summary, these structure–activity relationships suggest that mecamylamine is acting at a receptor. Evidence presented here and elsewhere suggests that mecamylamine, along with other secondary and tertiary amines, antagonize nicotine noncompetitively in the central nervous system.[6,7] Therefore, a separate receptor site may be responsible for nicotine antagonism in the CNS. It is possible that a receptor site could be located close to an ion channel such that bonding of an antagonist to this site could effectively block the action of nicotine by blocking the passage of ions through these channels.[19] Further elucidation of structural requirements of mecamylamine's actions may support the premise of distinctive receptors for nicotine agonists and antagonists.

Experimental Section

GC/MS analyses were obtained on a Hewlett-Packard 5988A GC/MS system by electron impact. IR spectra were taken on a Beckman AccuLab 8 spectrophotometer. ^{1}H NMR spectra were obtained on a JEOL FX90Q or GE QE300 spectrometers. Data obtained accommodated the structures in question but are tabulated only when vital for confirmation of structures and/or stereochemistry. Column chromatography was carried out on silica gel (E. Merck, particle size 0.063–0.02 mm). All thin-layer chromatography was carried out on precoated plates (silica gel 60 F-254, HLF). Optical rotations (at 22–25 °C) were obtained on a Perkin-Elmer Model 141 polarimeter. X-ray crystallography was performed at the Naval Research Laboratory with use of a Nicolet R3m/V Diffractometer and Nicolet SHELXTL PLUS software. Melting points are uncorrected. Chemical analyses were performed by Atlantic Microlab, Inc., and are within ± 0.4% of the theoretical values. Organic extraction solvents were dried over Na_2SO_4 unless otherwise noted.

Optical Resolution of Mecamylamine. A mixture of 2.0 g (12 mmol) of (±)-mecamylamine, base, 2.8 g (12 mmol) of (1*S*)-(+)-10-camphorsulfonic acid, and 45 mL of acetone was warmed to solution and cooled to room temperature (20 °C) during 2.5 h. The resulting solid (3.3 g, mp 211–213 °C) was dissolved in 90–100 mL of boiling acetone. The solution was concentrated on the hot plate to the appearance of needles (volume ca. 40 mL). After 2.5 h at 20 °C, 2.4 g of the camphorsulfonate salt, mp 211–213 °C, $[\alpha]_D$ +29.3° (*c* 0.69, absolute EtOH), was obtained. These values remained constant on further recrystallization. The HCl salt of (+)-mecamylamine was prepared in quantitative yield from the camphorsulfonate salt (ether–dilute NaOH, K_2CO_3 drying, HCl gas acidification). Recrystallized from 2-propanol, it melted at 271 °C (dec) and gave $[\alpha]_D$ +19.1° (*c* 1.23, $CHCl_3$). All acetone filtrates from the above operations were combined and evaporated to dryness in vacuo. The residue was converted to (±)- and (–)-mecamylamine bases (1.35 g, 8 mmol)) with dilute NH_4OH–ether and drying of the ether. Treatment of the free base (in 14 mL of Me_2CO) with 2.0 g of (1*R*)-(–)-10-camphorsulfonic acid gave 1.4 g of (–)-mecamylamine (1*R*)-(–)-10-camphorsulfonate needles; mp 210–211 °C; $[\alpha]_D$–28.7° (*c* 0.776, EtOH). The HCl salt of (–)-mecamylamine (see above for (+)-HCl salt) had mp 270 °C (dec) and $[\alpha]_D$ –19.0° (*c* 1.08, $CHCl_3$). Literature values are $[\alpha]_D$ +20.6° and –20.6° for the HCl salts and +31.2° for (1*S*)-(+)-10-camphorsulfonate of (+)-mecamylamine.[8] Brossi et al. who determined the absolute configuration of the antipodes reported $[\alpha]_D$ +20.1° and –20.0° for the HCl salts.[20]

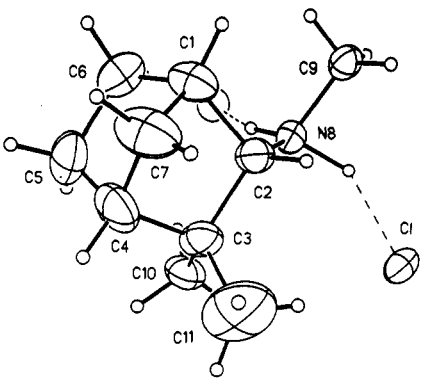

Figure 1. Thermal ellipsoid plot drawn from experimental coordinates of 3,3-dimethyl-*endo*-*N*-methylnorborn-2-ylamine (12) hydrochloride salt. Thermal ellipsoids are drawn at the 20% probability level. The dashed lines represent hydrogen bonds to the Cl anions. Unlabeled atom is a symmetry related anion.

Optical Purification of 30a and 30b Dihydrochlorides. A mixture of 0.5 g (1.9 mmol) of **30a** base (from the dihydrochloride using NH_4OH and ether), 0.45 g (1.9 mmol) of (1*S*)-(+)-10-camphorsulfonic acid and 3–4 mL of acetone was warmed to solution and treated with 5 mL of ether to give 0.5 g of the camphorsulfonate salt, mp 215–217 °C. Recrystallization from acetone gave material with a melting point of 221–222 °C and $[\alpha]_D$ +17.8° (*c* 2.65, EtOH); both values were unchanged on further recrystallization. The dihydrochloride of **30a**, prepared from the pure camphorsulfonate salt (aqueous NH_4OH–ether then HCl gas treatment of free base in acetone), melted at 228–229 °C, $[\alpha]_D$ –12.9° (*c* 1.2, EtOH). Similarly, **30b** (base) and (1*R*)-(–)-10-camphorsulfonic acid gave the corresponding camphorsulfonate salt (mp 221–222 °C, $[\alpha]_D$ –16.9° (*c* 1.01, EtOH)) and the dihydrochloride (mp 228–230 °C, $[\alpha]_D$ +14.2° (*c* 0.64, EtOH)).

X-ray Crystallography. The hydrochloride salts of **12** and **22** were examined. A clear colorless 0.015 × 0.40 × 0.52 mm data crystal of the HCl salt of **12** ($C_{10}H_{20}N^+ \cdot Cl^-$, fw = 189.7) was obtained by recrystallization from DMSO. A least-squares refine using 25 centered reflections within $23 < 2\theta < 52°$ gave the $P2_12_12_1$ orthorhombic cell a = 7.076 (6), b = 7.456 (9), c = 22.19 (2) Å, with V = 1172(2) Å^3, Z = 4, and D_{calcd} = 1.07 gm/cm^3. These data were collected with use of Cu Kα radiation, λ = 1.54184 Å. A total of 931 reflections were measured to a $2\theta_{max}$ = 112°, of which 911 were unique. No correction was made for absorption. The 124 parameters refined include atom coordinates and anisotropic thermal parameters for non-hydrogen atoms. The carbon hydrogen atoms were included at idealized locations and allowed to ride on covalently bonded atoms with C–H = 0.96 Å. Hydrogens bonded to nitrogen were refined isotropically with fixed thermal parameters. The maximum excursions for the final difference map were 0.60 and –0.40 eÅ^{-3}. The final R values for the 736 observed reflections were $F_o > 3\sigma|F_o|$ were R = 0.097, and R_w = 0.106, with g = 0.0005 (Figure 1).

A clear colorless 0.15 × 0.24 × 0.45 mm data crystal of **22** in the form of a hydrochloride salt ($C_9H_{18}N^+ \cdot Cl^-$, fw = 175.7) was obtained by recrystallization from 2-propanol. Data were collected on a computer-controlled diffractometer with an incident beam graphite monochromator (Siemens R3m/V with Mo Kα radiation, λ = 0.71073 Å, T = 295 K). A least-squares refinement using 25 centered reflections within $22 < 2\theta < 30°$ gave the $P\bar{1}$ triclinic cell a = 7.512 (2), b = 8.062 (2), c = 8.476 (2) Å, α = 97.56 (2), β = 100.85 (2), and γ = 93.01 (2)°, with V = 498.2 (2) Å^3, Z = 2, and D_{calcd} = 1.171 gm/cm^3. A total of 1645 reflections were measured in the $\theta/2\theta$ mode to $2\theta_{max}$ = 45° of which 1284 were unique (R_{int} = 1.38%). The scan width was [2θ(Kα_1) – 1.0] to [2θ(Kα_2) + 1.0]°, and scan rate was a function of count rate (3.5°/min minimum, 30.0°/min maximum in ω). Corrections were applied for Lorentz, polarization, and absorption effects. The

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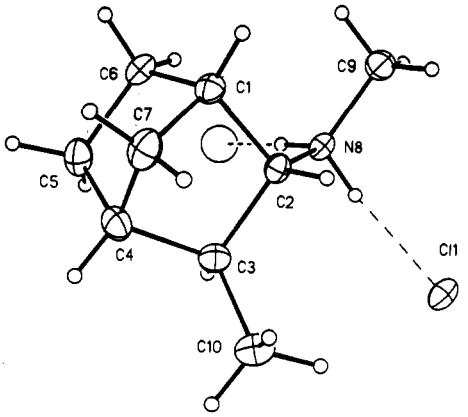

Figure 2. Thermal ellipsoid plot drawn from experimental coordinates of *exo*-3-methyl-*endo*-*N*-methylnorborn-2-ylamine hydrochloride salt. Thermal ellipsoids are drawn at the 20% probability level. The dashed lines represent hydrogen bonds to the Cl anions. Unlabeled atom is a symmetry related anion.

structure was solved by direct methods with the aid of the program SHELXTL[21] and refined with a full matrix least squares.[21] The 154 parameters refined include the coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogens were refined isotropically with fixed thermal parameters. Atomic scattering factors are from the *International Tables for X-ray Crystallography* (1974). The maximum excursions for the final Fourier difference map were 0.20 and -0.17 eÅ^{-3}. The final R values for the 1159 observed reflections with $F_o > 3\sigma|F_o|$ were $R = 0.033$, and $R_w = 0.042$, where $w = 1/[\sigma^2|F_o| + g(F_o)^2]$ and $g = 0.00023$ (Figure 2). Data collection and refinement parameters not given for **12** are identical with those of **22**.

The bond distances and angles for both **12** and **22** are normal. The poor quality of the thin crystal of **12** is responsible for the relatively high R values for the analysis and no attempt could be made to determine the absolute configuration. Compound **22** crystallized as a racemic mixture. Both salts formed a pair of hydrogen bonds between the quadrivalent nitrogen of each cation and the Cl anions. Tables of coordinates, bond distances and bond angles, have been deposited with the Crystallographic Data Centre, Cambridge, CB2, 1EW, England.

Pharmacology. Mecamylamine (**2a**) and its analogues were tested for antagonism of nicotine's ability to decrease spontaneous activity and its antinociceptive effect in mice. Mice were placed into individual photocell activity cages immediately after sc administration of either 0.9% saline, pH = 7.4 or (*S*)-(−)-nicotine di-L-tartrate. They were allowed to acclimate for 10 min. Data were expressed as % depression where: % depression = (counts from nicotine-treated animals/counts from saline-treated animals)100. Either antagonist or saline was administered sc 10 min prior to either saline or an ED_{84} dose of the nicotine ditartrate. The data were expressed as % antagonism where: % antagonism = [1 − (% effect with antagonist pretreatment/% effect with nicotine alone)]100.

Tail-flick reaction time to heat stimulus was determined following drug or saline administration using the method of D'Amour and Smith as modified by Dewey et al.[22] Preinjection, control values (2–4 s) were determined for all animals. Either antagonist or saline was administered sc 10 min prior to saline or nicotine bitartrate. Mice were retested 5 min after sc administration of either nicotine ditartrate or saline and the latency to the tail-flick response was recorded. A 10-s maximum latency was set to prevent tissue damage. Data were recorded as change in latency between pre- and post-injection testing for each animal. Data were expressed as % maximum possible effect (% MPE) where: % MPE = [(test latency − control latency)/(10-s control latency)]100.

The ED_{50} and AD_{50} values with 95% confidence limits (presented in parentheses) were determined by the method of Litchfield and Wilcoxon.[23] The potency ratios for each compound compared to (±)-*exo*-mecamylamine for spontaneous activity and antinociception were determined where: potency ratio = AD_{50} of compound/AD_{50} of (±)-*exo*-mecamylamine. The relative potency for each compound was calculated as the average of the potency ratios from spontaneous activity and antinociception.

Calculated Partition Coefficients. To estimate how alterations in the structure of mecamylamine (**2**) might effect biodistribution, the octanol–water partition coefficients of tested analogues were calculated by a procedure outlined by Rekker et al.[17] These values were considered when comparing the potencies of the different analogues. Calculated log P values were found to range from about 1.5 to 4.0.

***N*-Methylcamphenilimine (6).** Compound **5** (1.65 g, 12.0 mmol) was dissolved in 50 mL of toluene. Molecular sieves (4 Å, 20 mL) were added, and the mixture was brought to 120 °C. $MeNH_2$ was bubbled through this solution for 18 h. The cooled solution was filtered then applied to column chromatography eluting with CH_2Cl_2 to recover starting material (0.48 g). Elution with 5% MeOH in CH_2Cl_2 permitted an efficient isolation of product, observable in the column as a brown band (1.04 g, 6.89 mmol, 57% yield): GC/MS m/z (relative intensity) 151 (31), 136 (48), 108 (26), 82 (42), 55 (100); IR 2900, 1680, 1540, 1450 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3 H, s), 1.02 (3 H, s), 0.75–2.00 (8 H, m), 2.85 (3 H, s). The Picric acid salt recrystallized as heavy brown crystals from ethanol–ether (3:1), mp 212–216 °C. Anal. ($C_{16}H_{20}N_4O_7$) C, H, N.

Conversion of *N*-Methylcamphenilimine (6) to *N*-Methylisobornylamine (10). A mixture of **6** (0.790 g, 5.23 mmol) and 3 mL of MeI was refluxed for 10 min, then allowed to evaporate overnight to give a white, crystalline solid and an oily residue. The crystals (0.300 g) were isolated by rinsing with ether through a Buchner funnel and dissolved in warm CH_2Cl_2 in a 100 mL flask (N_2 atmosphere). To this solution was added (by syringe) 6.0 mL (8.4 mmol) of 1.4 M MeLi in ether. After 2 h the reaction mixture was quenched with 6 mL of MeOH–H_2O (1:1). The organic layer was washed with 2 × 25 mL of H_2O, dried, and evaporated to a brown oil (0.163g) that was applied to column chromatography eluting with CH_2Cl_2 followed by 10% MeOH in CH_2Cl_2 to give two components. The more polar component was not isolated in sufficient yield for complete characterization, and its HCl salt was very hygroscopic. GC/MS of this component, which did not coelute with **13**, indicated it to be *endo*-*N*-methylmecamylamine: m/z (relative intensity) 181 (14), 166 (12), 112 (100), 98 (54). The less polar component, isolated as a yellow oil (23 mg), was indicated by GC/MS and ^{1}H NMR to be *N*-methylcamphorimine (**11**): MS m/z (relative intensity) 165 (35), 150 (28), 95 (100), 83 (40), 57 (90); ^{1}H NMR (90 MHz, $CDCl_3$) δ 0.74 (s, 3 H), 0.92 (s, 3 H), 0.96 (s, 3 H), 1.00–1.98 (mm, 7 H), 3.04 (s, 3 H). This material was dissolved in MeOH and treated with excess $NaBH_4$. The reaction mixture was worked up in the usual fashion to give a new compound that was slightly more polar on TLC (using 10% MeOH in CH_2Cl_2) and was identified as *N*-methylisobornylamine (**10**), mp 289–292 °C, by spectral comparisons to a sample prepared from camphor: GC/MS m/z (relative intensity) 167 (24), 152 (8), 96 (100), 95 (70); IR 2860, 1450, 1365, 1260 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3 H, C-3 $CH_3(\beta)$), 0.99 (s, 3 H, C-3 $CH_3(\alpha)$), 1.10–1.32 (m, 3 H), 1.33–1.54 (m, 2 H), 1.55–1.78 (m, 3 H), 2.32 (m, 1 H, C-2 H), 2.34 (s, 3 H, C-1 NCH_3), 2.41 (s, 1 H, C-2 NH).

Conversion of Camphor to *N*-Methylisobornylamine (10). (±)-Camphor (0.930 g, 6.12 mmol) was dissolved in 30 mL of MeOH. $MeNH_2$ gas was bubbled through this solution for 15 min then left overnight. Aliquots were analyzed by GC/MS, which showed a 68% conversion to a component with a mass spectrum identical with *N*-methylcamphorimine (**11**), isolated above. This solution was treated with excess $NaBH_4$ for 30 min and then partitioned between H_2O and CH_2Cl_2. The organic layer was washed with 5% aqueous HCl, which was collected and basified with NaOH to pH 11 and extracted with CH_2Cl_2. This organic

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layer was dried and evaporated to a gold-colored oil (120 mg) shown by GC/MS to consist of two components (31% and 24%) with mass spectra identical with that observed for *N*-methylisobornylamine (**10**) as isolated above.

***endo*-2-Demethylmecamylamine (12).** *N*-Methylcamphenilimine (**6**) (1.1 g, 7.3 mmol) was dissolved in THF (50 mL) (distilled from Na–benzophenone), treated with LAH (362 mg, 9.54 mmol, 5.2 equiv), and refluxed for 3 h (N_2 atmosphere). The mixture was cooled to room temperature, quenched with 20 mL of 5% aqueous NH_4Cl, diluted with CH_2Cl_2, and washed with H_2O. The organic layer was dried and evaporated to an oil, which was diluted with anhydrous ether and treated with HCl gas. The resulting solid was recrystallized from 2-PrOH and ether to give the HCl salt of **12** as fine white crystals (330 mg, 1.74 mmol, 24% yield), mp 282–285 °C. Anal. ($C_{10}H_{19}ClN$) C, H, N. The free base was obtained by partitioning between CH_2Cl_2 and a saturated aqueous solution of $NaHCO_3$: GC/MS *m/z* (relative abundance) 153 (23), 110 (27), 84 (100), 70 (50); IR (neat) 2850, 2760, 1450, 1380 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.84 (s, 3 H), 1.00 (s, 3 H), 1.10–1.75 (m, 10 H), 2.30 (s, 1 H), 2.34 (s, 3 H), 2.42 (br s, 1 H).

(±)-*N*-Methylmecamylamine (13). (±)-Mecamylamine (**2a**) (375 mg, 2.25 mmol) was treated with 3 mL of MeI; crystals precipitated after several minutes. Excess MeI was allowed to evaporate, and the crystals were dissolved in 15% MeOH in CH_2Cl_2 and treated with NaOMe (500 mg) in MeOH (20 mL) with stirring for 15 min. This solution was treated with H_2O. The aqueous layer was washed with CH_2Cl_2. All organic layers were combined, dried, and evaporated to a yellow oil that was subjected to column chromatography with ether as eluent to give (±)-*N*-methylmecamylamine (**13**) (118.6 mg, 35% yield): GC/MS, *m/z* (relative abundance) 181 (18), 166 (10), 138 (22), 112 (100), 98 (40); IR (neat) 1455, 1430, 1380, 1360, 1253 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.94 (s, 3 H), 0.99 (s, 3 H), 1.00–1.75 (m, 8 H), 1.31 (s, 3 H), 2.34 (s, 6 H). HCl salt: mp 163–166 °C (hygroscopic). Anal. ($C_{12}H_{24}ClN$) C, H, N.

exo-*N*-Methylnorborn-2-ylamine (14). *exo*-2-Norbornylamine (2.5 g, 22.5 mmol) (Aldrich) in CH_2Cl_2 (20 mL) was added dropwise to 4-nitrophenyl chloroformate (PNPC) (4.67 g, 23.2 mmol) in CH_2Cl_2 (150 mL). Slight warming was noted and, after 8 h, solvent was evaporated in vacuo to a solid that was rinsed through a Buchner funnel with 5% aqueous HCl to remove unreacted amine followed by ether, in which PNPC is completely soluble and the desired carbamate, identified by TLC (R_f 0.47, CH_2Cl_2) is only partially soluble. Carbamate purified in this manner (1.00 g, 3.63 mmol) was dissolved in 15 mL of CH_2Cl_2 (distilled over CaH_2) and 135 mL of anhydrous ether and treated with LAH (140 mg, 3.69 mmol, 4 equiv) to give a bright yellow solution. After 1 h, the reduction was quenched by the slow addition of H_2O. The reaction mixture was diluted with CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$ to the point of colorless solutions. The organic layer was collected, dried, and evaporated to an oil shown by GC/MS to contain 85% of *exo*-*N*-methylnorborn-2-ylamine (**14**) (GC/MS *m/z* (relative abundance) 125 (87), 110 (17), 96 (100), 84 (83), 70 (76)) and 15% of the corresponding formamide (GC/MS *m/z* (relative abundance) 139 (50), 110 (25), 94 (100)). Greater quantities of the formamide were observed when greater proportions of CH_2Cl_2 were used as a solvent in the LAH reduction. The amine was isolated by column chromatography with CH_2Cl_2, MeOH, and NH_4OH (90:9:1) as eluent and recrystallized (from 2-PrOH) as the HCl salt (122 mg, 21% yield from reduction): mp 168–170 °C; TLC R_f 0.57, CH_2Cl_2–MeOH–NH_4OH, 40:9:1, IR (neat) 2940, 1255, 1090, 1020 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.02–1.13 (m, 4 H), 1.47 (br s, 6 H), 2.19 (br s, 2 H), 2.37 (s, 3 H), 2.37 (s, 3 H). Anal. ($C_8H_{16}ClN$), C, H, N.

***endo*-*N*-Methylnorborn-2-ylamine (15).** Prepared as above in similar yields from *endo*-norborn-2-ylamine (Aldrich) and recrystallized (from 2-PrOH) as the HCl salt: mp 166–169 °C; TLC R_f 0.66, CH_2Cl_2–MeOH–NH_4OH, 40:9:1; GC/MS *m/z* (relative abundance) 125 (87), 110 (17), 96 (100), 84 (83), 70 (76); IR (neat) 2940, 1260, 1090, 1020 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.15 (m, 1 H), 1.32 (m, 4 H), 1.50 (br s, 6 H), 2.13 (m, 1 H), 2.34 (s, 3 H). Anal. ($C_8H_{16}ClN$) C, H, N.

***N*,*N*-Dimethylisobornylamine (16).** *N*-Methylisobornylamine (**10**) (0.355 g, 2.13 mmol) was dissolved in 10 mL of MeOH, 10 mL of CH_2O, and 10 drops of formic acid. The warm reaction mixture was allowed to stand for 0.5 h, diluted with 60 mL of CH_2Cl_2, and washed with 0.1 M NaOH. The organic layer was collected, dried, and evaporated to an oil that was applied to a column of silica gel (230–400 mesh, 30 mm × 5 in.) and eluted with 5% MeOH in CH_2Cl_2 to give purified **16**, which was treated with HCl gas to give the HCl salt as an amorphous solid (54 mg, 12% yield): mp 156–161 °C (hygroscopic); GC/MS *m/z* (relative abundance) 181 (20), 166 (8), 138 (26), 112 (100), 98 (42); IR (neat) 1450, 1445, 1380, 1250, 1120 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.04–1.90 (m, 8 H), 0.89 (s, 3 H), 1.06 (s, 3 H), 1.20 (s, 3 H), 2.24 (s, 6 H). Anal. ($C_{12}H_{24}ClN$) C, H, N.

***exo*-3-Methyl-*endo*-*N*-methylnorborn-2-ylamine (22).** On a Parr hydrogenator, 3-methylene-2-norbornone, (**17**) (5.0 g, 41 mmol, Aldrich) and 1.0 g of 10% Pd/C in 100 mL ethanol absorbed 1 mol equiv of H_2 during a few minutes. Removal of catalyst followed by evaporation of solvent gave 4.5 g of a yellow oil containing two components with identical fragmentation patterns in a ratio of 96:4 as shown by GC/MS: *m/z* (relative abundance) 124 (40), 81 (58), 67 (100), 55 (90)). Attempts to epimerize by treatment with lithium diisopropyl amine were unsuccessful suggesting that the major isomer was the exo isomer **18** and the minor isomer was the endo isomer **19**. The hydrogenated material was applied to two columns of silica gel (230–400 mesh, 30mm × 6 in) with use of a solvent system of ether–petroleum ether (4:3) to give 3.09 g of more polar **18**, which was placed in a 100-mL round-bottom flask equipped with a stir bar, Dean–Stark trap, and condenser along with 7.0 mL of formamide (6 equiv) and 2 mL of formic acid. The reaction mixture was brought to 160 °C when bubbling and formation of brown color were observed. After 1.5 h, an additional 3 mL of formic acid was added and the reaction mixture was kept at 150 °C for 14 h. Upon cooling, a small top layer was observed. The mixture was partitioned between CH_2Cl_2 and H_2O (3×) and each washing of H_2O was washed with fresh CH_2Cl_2. All organic layers were combined, dried, and evaporated to a brown oil (3.27 g), containing two components, presumably isomers, with identical mass spectra in a ratio of 79:21 as indicated by GC/MS (*m/z* (relative abundance) 153 (40), 138 (20), 124 (14), 98 (100), 84 (60), 71 (40)). This material was dissolved in dry ether and combined with 1.09 g of LAH (5.4 equiv) under a N_2 atmosphere and refluxed overnight. The reduction was quenched with MeOH followed by H_2O. The resulting precipitate was filtered and washed with ether, and all organic layers were combined and evaporated to an oil that was partitioned between CH_2Cl_2 and 5% HCl. The aqueous layer was basified with KOH to pH >9 and extracted with CH_2Cl_2, which was dried and evaporated to a gold-colored oil (2.06 g) consisting of two components with identical mass spectra in a ratio of 79:21 (GC/MS, *m/z* (relative abundance) 139 (57), 124 (30), 96 (50), 84 (100), 70 (90)). The major component was isolated (1.060 g, 7.626 mmol, 18.6% yield from **17**) by column chromatography and found to be *exo*-3-methyl-*endo*-*N*-methylnorborn-2-ylamine (**22**) as shown by X-ray crystallography. HCl salt: mp 174–176 °C; IR (neat) 2930, 2830, 1450, 1410, 1255, 1110 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3 H, C-3 CH_3), 1.10–1.78 (m, 9 H), 2.21 (m, 2 H), 2.33 (s, 3 H, C-2 NCH_3). Anal. ($C_9H_{18}ClN$) C, H, N.

Formamidation of Optically Active Fenchone. In a typical reaction, optically active fenchone [(–) enantiomer from Aldrich, (+) enantiomer from Tokyo Asai] (35 g, 0.23 mol) and formamide (57.8 g, 1.28 mol, 5.6 equiv) were combined in a 250-mL round-bottom flask equipped with stir bar, thermometer, vigureux column, and Dean-Stark trap and kept at 160 °C for 16 h. Upon cooling, a solid formed. This material was washed with H_2O through a Buchner funnel and dissolved in CH_2Cl_2. This solution was dried and evaporated to a white crystalline solid (33.75 g, 81% yield) determined (by GC/MS) to contain the epimers of *N*-formylfenchylamine (**24**) in a ratio of 98:2. Mass spectra for these epimers were identical: GC/MS *m/z* (relative intensity) 181 (7), 166 (4), 136 (32), 101 (62), 81 (100). The predominant epimer of **24** was determined to be the endo isomer by X-ray crystallography of the *N*-nicotinoyl derivative **30** (C. George, unpublished). Spectral and physical data for **24** were obtained without separation of the epimers: IR (neat) 2900, 2840, 1640, 1530, 1455, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.82 (s, 3 H), 1.00 (s, 3 H), 1.04 (s, 3 H), 1.05–1.88 (m, 7 H), 3.70 (d, 1 H, C-2 H), 6.50

(br s, 1 H, C-2 NH), 8.35 (s, 1 H, C-2 NCOH). From (+)-fenchone, **24a**: $[\alpha]_D$ −64.9° (*c* 0.635, EtOH); mp 106–108 °C. Anal. ($C_{11}H_{19}NO$) C, H, N. From (−)-fenchone, **24b**: $[\alpha]_D$ +63.4° (*c* 0.595, EtOH); mp 103–105 °C. Anal. ($C_{11}H_{19}N$) C, H, N.

Optically Active Isomers of *endo*- and *exo*-*N*-Methylfenchylamine (25 and 26, Respectively). In a typical reaction, **24** (5.75 g, 31.8 mmol) in ether was treated with LAH (2.040 g, 3.38 equiv) and the mixture refluxed overnight. Reduction was quenched by the slow addition of MeOH, followed by H_2O. Precipitates were filtered and rinsed with CH_2Cl_2. All "organics" were combined, dried, and evaporated to a colorless oil (4.50 g), which was dissolved in ether and treated with HCl gas to give insoluble salts of the epimers of *N*-methylfenchylamine, which were collected by filtration (4.55 g, 70.3% yield). This material was converted to the free base and separation of the epimers was performed by column chromatography with use of silica gel (230–400 mesh) and ether as eluent, giving 3.46 g of the less polar and predominant endo isomer **25** and 0.75 g of an oil containing the endo and exo isomers in a ratio of 71:29, respectively. Additional column chromatography gave 59 mg of the exo isomer **26**. The mass spectra of these compounds were identical: GC/MS *m/z* (relative abundance) 167 (18), 152 (5), 136 (32), 98 (58), 84 (60); (from **24a** and **25a** (HCl salt)) $[\alpha]_D$ +0.6° (*c* 1.01, EtOH); mp 252–257 °C, (free base $[\alpha]_D$ −47.2° (*c* 1.85, EtOH)); (from **24b** and **25b** (HCl salt)) $[\alpha]_D$ −0.7° (*c* 1.113, EtOH); mp 267–270 °C, (free base $[\alpha]_D$ +38.6° (c, 1.50, EtOH)); IR (neat) 2915, 2850, 2770, 1460, 1362 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.85 (s, 3 H), 0.98 (s, 3 H), 1.03 (s, 3 H), 0.95–1.03 (m, 2 H), 1.25–1.50 (m, 3 H), 1.60 (m, 2 H), 2.00 (s, 1 H, C-2 NH), 2.40 (s, 3 H, C-2 NCH_3); (from **24a** and **26a** (HCl salt)) $[\alpha]_D$ −21.0° (*c* 0.319, EtOH); mp 280–283 °C; (from **24b** and **26b** (HCl salt)) $[\alpha]_D$ +3.64° (*c* 0.467, EtOH); mp 267–270 °C; IR (neat) 2900, 2850, 2770, 1455, 1350 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.98 (s, 3 H), 0.99 (s, 3 H), 1.30 (s, 3 H), 0.70–1.80 (m, 8 H), 2.00 (s, 1 H, C-2 NH), 2.35 (s, 3 H, C-2 NCH_3). All isomers anal. ($C_{11}H_{22}ClN$) C, H, N.

Preparation of *N*-(3-Methylenepyridyl)fenchylamine Analogues. Optical antipodes of **24** were individually hydrolyzed, treated with 3-pyridinecarboxaldehyde, and reduced to give the endo and exo isomers of *N*-(3-methylenepyridyl)fenchylamine, **28** and **29**, respectively. In a typical hydrolysis, **24** (14.39 g, 79.5 mmol) was refluxed for 3 h in 100 mL of H_2O and 100 mL of concentrated HCl. The solution was cooled to room temperature, washed 3 times with CH_2Cl_2, basified to pH 12 with NaOH (50 g in 100 mL of H_2O added dropwise at 0 °C), and extracted four times with CH_2Cl_2. The combined extracts were dried and evaporated to an oil (2.65 g, 17.3 mmol, 22% yield). From **24a** and **27a** (HCl salt): $[\alpha]_D$ −7.2° (*c* 0.580, EtOH); mp >275 °C, (free base $[\alpha]_D$ −22.4° (*c* 0.205, EtOH)). From **24b** and **27b** (HCl salt): $[\alpha]_D$ +3.6° (*c* 1.020, EtOH); mp >270 °C, (free base $[\alpha]_D$ +17.0° (*c* 1.506, EtOH)). Both isomers anal. ($C_{10}H_{20}ClN$) C, H, N. In a typical condensation reaction, **27** (1.87 g, 12.2 mmol) was mixed with 3-pyridinecarboxaldehyde (1.31 g, 15.4 mmol) without solvent and brought to 115 °C for 5 min to remove H_2O. Reaction material crystallized upon cooling (GC/MS *m/z* (relative abundance) 242 (26), 241 (19), 199 (22), 161 (100)) was dissolved in MeOH (75 mL) and treated with $NaBH_4$ (1.050 g, 7.2 equiv) over a 2-h period. After quenching by the addition of 5% HCl (aqueous), the reaction mixture was partitioned between H_2O and CH_2Cl_2. Organic layers were combined, dried, and evaporated to a gold-colored oil (3.49 g, 14.3 mmol, 93% yield) shown by TLC and GC/MS to contain endo and exo epimers of *N*-(3-methylenepyridyl)fenchylamine, **28** and **29**, respectively. This material was applied to a column of silica gel (230–240 mesh, 25 mm × 5 in) and eluted with ether and CH_2Cl_2 (50:50) to give **28** (1.215 g) and **29** (25.6 mg). From **24a** and **28a** (2 HCl salt): $[\alpha]_D$ +4.64° (*c* 1.79, 9 EtOH:1 H_2O); mp >270 °C. From **24b** and **28b** (2 HCl salt): $[\alpha]_D$ −4.74° (*c* 2.89, 9 EtOH:1 H_2O); mp >270 °C; IR (neat) 3010, 2870, 1570, 1450, 1360 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3 H), 1.09 (s, 3 H), 1.15 (s, 3 H), 1.00–1.15 (m, 2 H), 1.27–1.55 (m, 3 H), 1.65 (m, 2 H), 2.20 (s, 1 H, C-2 NH), 3.80 (dd, 2 H, C-2 NCH_3), 7.25 (m, 1 H, C-5′H), 7.70 (d, 1 H, C-4′H), 7.99 (d, 1 H, C-6′H), 8.10 (s, 1 H, C-2′H). From **24a** and **29a** (2 HCl salt): $[\alpha]_D$ +7.7° (*c* 0.89, EtOH); mp 267–270 °C. From **24b** and **29b** (2 HCl salt): $[\alpha]_D$ −6.4° (*c* 0.57, EtOH); mp 270–275 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 1.00 (s, 3 H), 1.01 (s, 3 H), 1.10 (s, 3 H), 0.95–1.52 (m, 5 H), 1.65 (m, 2 H), 2.20 (s, 1 H, C-2 NH), 3.83 (dd, 2 H, C-2 NCH_2), 7.25 (m, 1 H, C-5′H), 7.57 (d, 1 H, C-4′H), 8.00 (d, 1 H, C-6′H), 8.10 (s, 1 H, C-2′H). All isomers except **29b** anal. ($C_{16}H_{26}ClN_2$) C, H, N. The *N*-methyl derivatives of **28**, compounds **30a** and **30b**, were prepared by treatment with formaldehyde and formic acid as described for the formation of **16**: GC/MS *m/z* (relative abundance) 258 (1), 243 (4), 189 (36) 135 (100). From **28a** and **30a** (2 HCl salt): $[\alpha]_D$ +14.2° (*c* 0.643, EtOH); mp 228–230 °C (free base $[\alpha]_D$ −21.0° (*c* 1.140, EtOH) (1*R*)-(−)-10-camphorsulfonate salt $[\alpha]_D$ −17.5° (*c* 2.61, EtOH); mp 221–222 °C). From **28b** and **30b** (2 HCl salt): $[\alpha]_D$ −12.9° (*c* 1.20, EtOH); mp 227–229 °C (free base $[\alpha]_D$ −21.0° (*c* 1.422, EtOH)), (1*S*)-(+)-10-camphorsulfonate salt $[\alpha]_D$ +17.7° (*c* 2.61, EtOH); mp 221–222 °C); IR (neat) 3010, 2900, 2760, 1570, 1455, 1370 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 3 H), 1.10 (s, 3 H), 1.35 (s, 3 H), 1.00–2.05 (m, 8 H), 2.05 (s, 3 H), 2.50 (s, 1 H, C-2 NH), 3.50 (dd, 2 H, C-2 NCH_3), 7.45 (m, 1 H, C-5′H), 7.75 (d, 1 H, C-4′H), 7.48 (d, 1 H, C-6′H), 8.60 (s, 1 H, C-2′H). HCl salts anal. ($C_{17}H_{28}ClN_2$) C, H, N. Camphorsulfonate salts anal. ($C_{37}H_{58}N_2O_8S_2$) C, H, N.

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Registry No. (±)-**2a**, 6147-18-8; **2b**, 107538-06-7; **2b**·HCl, 107596-31-6; **2b**·(1*R*)-(−)-10-camphorsulfonate, 131348-12-4; **2c**, 107538-05-6; **2c**·HCl, 107596-30-5; **2c**·(1*S*)-(+)-camphorsulfonate, 131348-05-5; (±)-**4**, 565-00-4; (±)-**5**, 52363-25-4; (-)-**6**, 131274-89-0; (±)-**8**, 131274-90-3; (±)-**9**, 21368-68-3; (±)-**10**, 129785-05-3; (±)-**11**, 131347-96-1; (±)-**12**, 129721-89-7; (±)-**12**·HCl, 131274-95-8; (±)-**13**, 131274-92-5; (±)-**13**·HCl, 131274-96-9; (±)-**14**, 131274-93-6; (±)-**14**·HCl, 131274-97-0; (±)-**15**, 78940-80-4; (±)-**15**·HCl, 131274-98-1; (±)-**16**, 129777-16-8; (±)-**16**·HCl, 131274-99-2; (±)-**17**, 118626-62-3; (±)-**18**, 120410-05-1; (±)-**19**, 131347-97-2; (±)-**20**, 131274-94-7; (±)-**21**, 131347-98-3; (±)-**22**, 131347-99-4; (±)-**22**·HCl, 131432-13-8; **23a**, 4695-62-9; **23b**, 7787-20-4; *exo*-**24a**, 131348-08-8; *endo*-**24a**, 131348-00-0; *exo*-**24b**, 131348-09-9; *endo*-**24b**, 131348-04-4; **25a**, 129721-92-2; **25a**·HCl, 131483-48-2; **25b**, 129721-93-3; **25b**·HCl, 131483-54-0; **26a**, 129721-90-0; **26a**·HCl, 131483-53-9; **26b**, 129721-91-1; **26b**·HCl, 131483-55-1; *exo*-**27a**, 131348-10-2; *endo*-**27a**, 131348-01-1; *exo*-**27a**·HCl, 131432-19-4; *endo*-**27a**·HCl, 131432-14-9; *exo*-**27b**, 131348-11-3; *endo*-**27b**, 131348-06-6; *exo*-**27b**·HCl, 131432-20-7; *endo*-**27b**·HCl, 131432-25-2; **28a**, 129722-00-5; **28a**·2HCl, 131483-49-3; **28b**, 129721-99-9; **28b**·2HCl, 131483-50-6; **29a**, 129721-98-8; **29a**·2HCl, 131483-51-7; **29b**, 129741-39-5; **29b**·2HCl, 131483-52-8; **30a**, 13148-02-2; **30a**·2HCl, 131432-15-0; **30a**·(1*R*)-(−)-10-camphorsulfonate, 131432-17-2; **20b**, 131348-07-7; **30b**·2HCl, 131432-16-1; **30b**·(1*S*)-(+)-10-camphorsulfonate, 131432-18-3; (±)-**31**, 131348-03-3; 4-$O_2NC_6H_4OCOCl$, 7693-46-1; nicotinaldehyde, 500-22-1.