Effects of Addition of a 2-Methyl Group to Ethyl Nipecotates (β-Meperidines) on Receptor Affinities and Opiate Agonist/Antagonist Activities

John A. Lawson,* Alice Cheng, Joseph DeGraw, Gernot Frenking, Edward Uyeno, Lawrence Toll, and Gilda H. Loew

SRI International, Menlo Park, California 94025. *Received September 14, 1987*

A series of 2-methyl-3-carbethoxy-3-(*m*-hydroxyphenyl)piperidine opiates (**13a–d**) with N-substituent variations have been synthesized, and their receptor affinities and in vivo agonist and antagonist activities and energy-conformational profiles have been determined. These are racemates of the α-epimer at the C-2 position, with a methyl group cis to the 3-phenyl group. One of the main goals of this study was to compare the conformational and pharmacological behavior of these 2-methyl "β-meperidine" analogues to their 2-desmethyl racemic counterparts (**14a–c**) previously reported in the literature. The 2-desmethyl and 2-methyl analogues were found to have very similar phenyl equatorial conformers as their lowest energy forms with the addition of a 2-methyl group diminishing conformational flexibility. The presence of the 2-methyl group appears to diminish affinity at the μ-receptor and also to somewhat diminish already weak antinociceptic agonist activity. Given the similarity in lowest energy conformation, this reduction is most likely caused by the unfavorable interaction of the methyl group itself with a local μ-receptor binding site. Superposition of the phenol OH and protonated amine nitrogen NH of either 2-methyl enantiomer of **13a** in its lowest energy conformer with the same OH and NH groups of metazocine, used as a high affinity rigid analogue, leads to reasonable overlap. However, the N-substituents and the piperidine and phenyl rings do not overlap in this proposed pharmacophore, perhaps accounting for the rather poor affinities found for these 3-phenylpiperidines and the lack of N-substituent modulation of affinity and efficacy as in fused ring opioids.

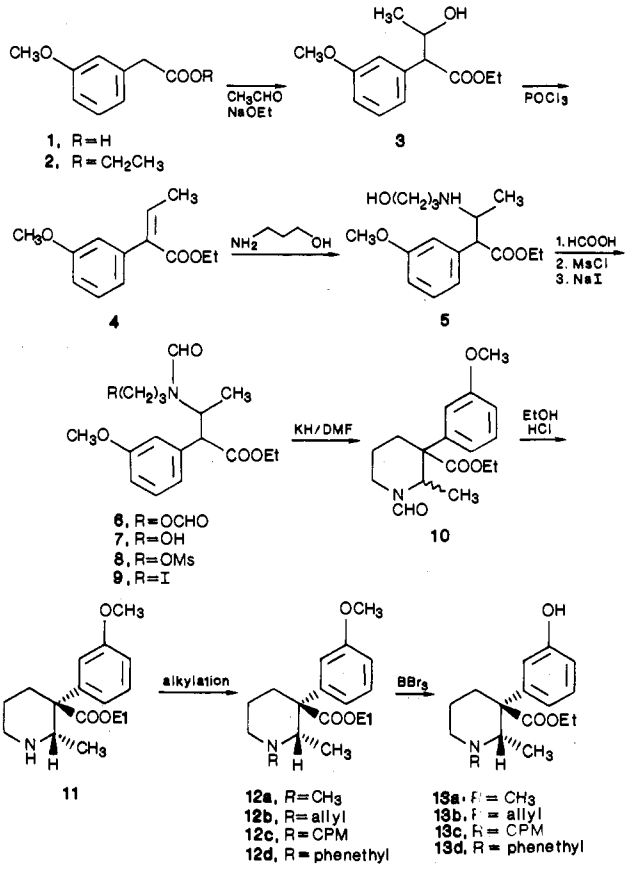
3-Phenylpiperidines (3PPs) are a novel family of flexible opioids.[1-5] While they incorporate the phenethylamine functionality found in all morphine-related opiates and the tyrosine portion of the enkephalins, the 3PPs are not a fragment of morphine, since the piperidine ring and the phenyl ring cannot both overlap the corresponding structures in morphine. As a result, the structural and conformational relationships of the phenyl group to the piperidine ring and its other substituents differ from the analogous relationships in the more widely studied 4-phenylpiperidines (4PPs), which are a morphine fragment.

For many years, efforts to synthesize antagonists in both 3- and 4-phenylpiperidines, mainly by N-substituent variations such as *N*-allyl and cyclopropylmethyl, were unsuccessful. One common discovery in the two series was that a *m*-OH substituent on the phenyl ring results in the development of analgesic antagonism. Moreover, the most potent antagonists in the 4PP series are 4-methyl derivatives with a trans-axial 3-methyl group[6] while, in the 3PP series, the most potent antagonists are 3-methyl derivatives with a trans-axial 2-methyl group.[3]

In a recent study[5] we have investigated the question of whether antagonism can be preserved in the 3-methyl-3-(*m*-hydroxyphenyl)piperidines in the absence of a 2-methyl group and how agonist/antagonist activity is modulated in this family by N-substituent variation. In that study we found significant differences in μ-receptor affinities for the resolved enantiomers and differences in efficacy as well. The (+) enantiomers were pure antagonists, while the (−) enantiomers had both agonist and antagonist activity. Unlike the fused ring opiates, the *N*-phenethyl derivative was the most potent antagonist, about 17% that of nalorphine. Based on an X-ray structure determination of the active (+) enantiomer and on the pharmacological and energy conformation studies, we proposed a phenyl equatorial conformer overlapping with the *m*-hydroxyphenyl group of morphine as the antagonist pharmacophore.

Synthesis and pharmacological testing has also been reported[4,5,7] for a second 3PP family, the so-called β-meperidines with a 3-carbethyoxy substituent, isomeric

Scheme I



(1) Kugita, H.; Inoue, H.; Oine, T.; Hayashi, G. *J. Med. Chem.* **1965**, *8*, 313.
(2) Casy, A. F.; Iorio, M. A. *Gazz. Chim. Ital.* **1974**, *104*, 655.
(3) Iorio, M. A.; Casy, A. F. *J. Med. Chem.* **1978**, *21*, 812.
(4) Jacoby, R. L.; Boon, D.; Darling, L. E.; Willette, R. E. *J. Med. Chem.* **1981**, *24*, 218.
(5) Cheng, A.; Uyeno, E.; Polgar, W.; Toll, L.; Lawson, J. A.; DeGraw, J. I.; Loew, G. H.; Camerman, A.; Camerman, N. *J. Med. Chem.* **1986**, *29*, 531.
(6) Zimmerman, D. M.; Smitz, S. E.; Hynes, M. D.; Cantrell, B. E.; Reamer, M.; Nickander, R. Proceedings of the 43rd Annual Meeting of the Committee on Problems of Drug Dependence; 1981, p 112.
(7) Jacoby, R. L.; Nieforth, K. A.; Willette, R. E. *J. Med. Chem.* **1974**, *17*, 453.

0022-2623/88/1831-2015$01.50/0

with the 4PP analogue meperidine. Pharmacological evaluation of racemates of this series, with either *m*-hydroxy- or *p*-hydroxyphenyl group and with N-substituent variation, indicated that the presence of a *m*-OH group produced weak, nearly pure antagonists.[4,5,7] We subsequently performed receptor-binding studies of these compounds and found them to be μ-selective with moderate affinities.[8]

In contrast to our study of the effect of removal of a 2-methyl in 2,3-dimethyl-3PPs, the study reported here focuses on the effect of addition of a 2-methyl group to 3-carbethoxy-3-(*m*-hydroxyphenyl)-β-meperidine analogues. Thus, we have synthesized four 3PP compounds with the same 3-CO_2Et group as previously reported but with a 2-CH_3 group cis to the *m*-hydroxyphenyl group and with four N-substituents: methyl (**13a**), allyl (**13b**), cyclopropylmethyl (**13c**), and phenethyl (**13d**) as shown in Scheme I. Detailed receptor binding studies and determination of in vivo agonist and antagonist potencies have been made for these analogues and compared with their corresponding des-2-CH_3 compounds (**14a**, *N*-methyl; **14b**, *N*-allyl; **14c**, *N*-cyclopropylmethyl). In addition, energy-conformational studies have been made for the *N*-methyl analogues with C-2 substituents: des-2-methyl (**14a**); *cis*-CH_3 (**13a**); and *trans*-CH_3 (**15a**) to further probe the effect of the 2-CH_3 group. Unfortunately, synthetic difficulties precluded the resolution of these new β-meperidines. Thus, the binding and relationship of activity to structure that we previously reported for resolved 3-methyl analogues is not possible. However, since the parent 2-H β-meperidines were reported as racemates,[4] the studies presented here should allow an even-handed determination of the effect of addition of a 2-methyl group on the affinity and activity of these two β-meperidine families.

Methods and Materials

1. Chemistry. The reaction sequence shown in Scheme I commenced with esterification of commercially available 3-(*m*-methoxyphenyl)acetic acid (**1**) with ethanolic hydrogen chloride to give the ethyl ester **2**. Hydroxyalkylation of **2** according to the general procedure of Schwenker and Berber[9] in the presence of acetaldehyde and the basic catalyst sodium ethoxide yielded ethyl 2-(*m*-methoxyphenyl)-3-hydroxybutanoate (**3**). Dehydration of **3** with phosphorus oxychloride in pyridine furnished a mixture of cis and trans unsaturated esters **4**. Treatment of these unsaturated esters with 3-aminopropanol generated the Michael product **5**. Initial attempts to react **5** with ethyl formate under reflux conditions led to the formation of the N-formylated analogue **7**. However, this reaction required 2 days for completion, during which time a substantial amount of reverse Michael product was formed. Instead, treatment of **5** with a mixture of formic acid and acetic anhydride at 60 °C provided a good yield of the N,O-diformylated compound **6** in 2 h; no reverse Michael reaction could be detected. Selective cleavage of the oxyformyl with sodium bicarbonate at room temperature afforded compound **7**. This intermediate was allowed to react with methanesulfonyl chloride to generate the unstable mesylate **8**, which in the presence of NaI in acetone rapidly afforded the iodide **9**, stable at −40 °C.

Cyclization of **9** with KH/DMF gave **10** as a diastereomeric mixture in 30% yield. The reverse Michael reaction was demonstrated to be the major direction of this reaction by the fact that the unsaturated ester **4** was the major product isolated.

NMR analysis of **10** revealed that this ring cyclization gave a diastereomeric mixture in which one diastereomer (2-α-methyl, **10**α) predominated over the other, forming about 70% of the mixture. The *cis*-2-methyl-3-aryl, 10α, and *trans*-2-methyl-3-aryl, **10**β, stereochemistries were preliminarily assigned based on NMR shielding effects, similar to those observed by Kugita and Iorio[2] on similar compounds having known stereochemistry. Thus, the NMR spectrum of **10**α and **10**β in $CDCl_3$ displayed two sets of doublets centered at δ 1.27 and 1.40, having a coupling constant, J = 6.8 Hz, for the C_2-methyl protons; two sets of quartets centered at δ 4.63 and 5.53 (J = 6.8 Hz) for the C_2-methine signals (ratio of 3:7), and two singlets at δ 7.96 and 8.19 for the formyl proton signals (ratio of 7:3). The large difference in the chemical shift (0.9 ppm) between the two methine protons of **10**α and **10**β and their relative downfield shift from the ring-opened starting material can be attributed to the unsymmetrical magnetic anisotropic environment about the two positions in diastereomers **10**α and **10**β. Examination of the Dreiding model of the diastereomers **10**α indicated that the C_2-methine proton in *cis*-**10**α lies in the deshielding region caused by the diamagnetic anisotropy of the carbonyl groups (formyl and ester) resulting in the downfield signal at δ 5.53 (the major quartet). In contrast, the C_2-methyl protons of **10**α are situated such that they experienced the shielding effect of *N*-formylcarbonyl, thus accounting for the upfield absorption at δ 1.27 (the major doublet). Compound **10**α therefore represented the major diastereomer that was formed. By the same token, one can account for the chemical shifts that we observed for the minor diastereomer, **10**β (2-β-CH_3). In this case the C_2-methine proton was situated such that it was shielded by the formylcarbonyl and the signal appeared at δ 4.63 (the upper field quartet), whereas the C_2-methyl protons were deshielded and their signals corresponded to that at δ 1.40 (the lower field doublet).

The hydrolysis of the *N*-formyl group proceeded smoothly to give **11**α,β. The reaction was monitored by the disappearance of the *N*-formyl signals and the upfield shift of the 2-methine quartets. The diastereomeric forms of **11**α,β was demonstrated by ^{13}C NMR analysis with major signals representing the α-form and satellite peaks (adjacent to the major ones) corresponding to the β-form. An analytically pure sample was obtained by conversion to the HCl salt followed by recrystallization. When the bases **11**α,β were converted to the picrate salts and recrystallized, only one diastereomer was recovered; this was confirmed by the ^{13}C NMR spectrum of the free base, which showed the presence of only one diastereomer (±)-**11**α. On the basis of the weight of the recovered material, this was assigned the major 2-α-CH_3 diastereomer. ^{13}C NMR spectroscopy was relied upon as a primary standard for the separation of this major diastereomer. N-alkylation of this α-racemate followed by O-demethylation with BBr_3 successfully achieved the desired final products (±)-**13a–d**.

A recent careful NMR study[10] of a closely related 3-ϕ family, the 2,3-dimethyl-3-(*m*-methoxyphenyl)piperidines (α- and β-diastereomers) guided us in our confirmation of the relative configurations at C-2 and C-3, as well as the conformation of these substituents. Thus, when the C-2 methyl doublet (1.06 ppm) of **13a** as free base was irradiated in an NOED experiment, the ortho aromatic protons showed enhancement (1.3% for C-2′), consistent with

(8) Toll, L.; Keys, C.; Loew, G. *Life Sci.* **1983**, *33* (Suppl 1), 427.
(9) Schwenker, G.; Berber, R. Chem. Ber. **1967**, *100*, 2460.
(10) Casy, A. F.; Iorio, M. A.; Madani, A. E. *Magn. Reson. Chem.* **1987**, *25*, 524–530.

a cis configuration. In addition, the N-CH_3 protons showed a 0.8% enhancement. With regard to the conformation of the C-2 methyl, the study cited above[10] found that the ^{13}C NMR signals for an axial-α (cis to equatorial phenyl)-2-methyl carbon falls in the range of 5.8–7.0 ppm, while the diastereomeric β-isomer (equatorial)-2-methyl carbon is found at 14–14.5 ppm. In **13a** the ^{13}C chemical shift for the α-methyl is 7.5 ppm, consistent with the α-(axial) conformation. Further evidence for this assignment is the shielding of C-4 by the axial 2-methyl wherein C-4 resonances are at higher field (25.2–26.2 ppm) in the α-diastereomer than in the β (38.1–38.7 ppm).[10] The chemical shift assignment for C-4 in **13a** is at 27.2 ppm, in the range expected for an axial-2-methyl effect.

Comparison of the ^1H spectrum of **13a** with that of the des-2-methyl analogue **14a** revealed, for the most part, few major differences. Compound **14a** has a second C-2 proton which falls at δ 2.26 (partially under the N-CH_3 peak). No long-range coupling of either H-2 proton in **14a** or the H-2 proton in **13a** to a H-4 or H-6 proton was observed, unlike the reported[4] long-range coupling of the lower field C-2 proton at 3.74 ppm to a H-4 or H-6 proton in the N-normethy-m-methoxy analogue of **14a**. If this reported long-range coupling is via a W-pathway,[11] then the protons involved are both equatorial, and the downfield H-2 proton in the N-normethyl analogue mentioned above is equatorial, not axial as proposed.[4] This is consistent with our assignment of the C-2 methyl in **13a** to an axial conformation, and the remaining C-2 proton at low field (3.52 ppm) to an equatorial position.

The NMR spectra of **13a–d** as HCl salts in $CDCl_3$ showed evidence of the presence of two conformers. This was most clearly observed by **13c**·HCl in which there were two overlapping aromatic patterns, consistent with the expected m-hydroxyphenyl (two pairs of ortho-coupled protons due to C-4′, C-6′, one pair of bis(ortho)-coupled triplets due to C-5′, and two broad singlets due to C-2′). We ascribe these effects to the presence of both the phenyl equatorial and phenyl axial conformers. The protons on the axial m-hydroxyphenyl group axial are 0.12–0.18 ppm higher field than the equatorial aromatic protons. In spite of the fact that our calculations suggest that the equatorial form would be present almost exclusively in the gas phase, these NMR data indicate that in $CDCl_3$ both conformers are present in significant populations; the equatorial exceeding the m-hydroxyphenyl axial conformer population by only a 5:1 ratio for **13a**·HCl, 4:1 for **13d**·HCl, 3:1 for **13b**, and are equivalent (1:1) for **13c**·HCl (the N-CPM derivative). Thus, it appears that interactions between the solvent ($CDCl_3$) and the protonated amine salt can selectively stabilize the axial conformer vis à vis the equatorial, and these effects are to a degree modulated by the N-substituent.

2. Opiate Receptor Binding Assay and Data Analysis. Receptor binding studies were conducted in rat brain membranes as described previously.[5] Briefly, rats were killed by cervical dislocation, and brains were rapidly removed. The brains were homogenized in Tris buffer, pH 7.7, and centrifuged at 40000g for 15 min. The pellets were suspended in Tris buffer and incubated at 37 °C for 1 h to remove any endogenous opioids. The membranes were centrifuged once more and resuspended in Tris buffer. Incubations consisted of 12 mg of tissue and the appropriate tritiated and unlabeled opiate in a total volume of 2.0 mL. Samples were incubated for 1 h at 25 °C prior to filtration. Filters were placed in plastic minivials to which 5 mL of scintillation cocktail was added. Samples were left in the cocktail overnight prior to counting.

To determine affinities at μ and δ, each unlabeled opioid, including the four partners of the labeled ligands used and the seven β-meperidine analogues, were used to inhibit binding of [^3H]DHM, [^3H]DADL, [^3H]DSLET, and [^3H]EKC. In each experiment, nonspecific binding was determined in the presence of 1.0 μM of a nonradioactive form of the tritiated ligand used in that experiment. Each inhibition curve was repeated twice at two labeled ligand concentrations. All the data were then analyzed simultaneously by using the curve-fitting program LIGAND,[12] as described previously.[5]

Once binding studies in rat brain were begun, it became clear that affinity at κ-receptors could not be properly characterized due to the very low level of κ-receptors in rat brain. To determine affinities at κ, binding studies were conducted in guinea pig brain membranes because this tissue was shown to possess high levels of κ-receptors.[13] Binding studies were conducted as described for rat brain with [^3H]U69,593, a ligand selective for κ-receptors.[14] K_D values at κ were also determined using LIGAND. Previous studies have shown that the affinity of a particular compound at μ, δ, and κ sites is similar in rat and guinea pig brain (Toll et al., submitted for publication). Thus, this cross-species comparison should provide accurate values for affinity at μ-, δ-, and κ-receptors.

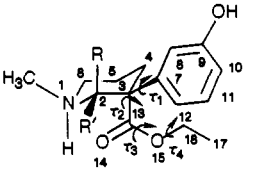
The des-2-methyl analogues **14a–c** were kindly supplied by Dr. Willette.

3. Animal Testing. a. Agonism. Male Swiss–Webster mice weighing 21–28 g were housed in conventional plastic cages in a temperature- (22.5 ± 2 °C) and humidity-controlled laboratory with 12 h of light (0700–1900 hours) per day. Prior to medication, they were pretested twice in a tail-flick assay,[15,16] which we have adapted. The heat lamp was set to induce a tail-flick reaction in 2–4 s. After determining an effective analgesic dose range for each compound, time-course and dose–response experiments (three doses/compound; 10 animals/dose) were conducted. The animals was injected subcutaneously with a test chemical, standard, or diluent, and the tail-flick test was administered at 10, 20, 30, 45, and 60 min after treatment. A 6.5-s cut-off time for tail-flick response was used; 6.5 s minus the reaction time of the control group was considered to be the maximum possible increase in response time.[16] At the time of peak effect of each dose, the average increase in response time of each treated group was determined and the percent of the maximum possible increase in reaction time (percent agonism) was computed. The percentages were plotted versus the log dose on probit paper, and the median effective dose (ED_{50}) and the 95% confidence limits were calculated by the method of Litchfield and Wilcoxon.[17]

b. Antagonism. Antagonist activity of the compounds against 8 mg/kg (21.08 μmol/kg; ED_{80}) of morphine sulfate was determined by the tail-flick procedure. Mice were injected subcutaneously (sc) with a test substance, reference drug, or vehicle only and given immediately 8 mg/kg

(11) Sternhell, S. *Rev. Chem. Soc.* **1969**, *23*, 236.
(12) Munson, P. J.; Rodbard, D. *Anal. Biochem.* **1980**, *107*, 220.
(13) Kosterlitz, H. W.; Paterson, S. J.; Robson, L. E. *Br. J. Pharmacol.* **1981**, *73*, 939.
(14) Lahti, R. A.; Mickelson, M. M.; McCall, J. M. Von Voightlander, P. F. *Eur. J. Pharmacol.* **1985**, *109*, 281.
(15) D'Amour, F. E.; Smith, D. L. *J. Pharmacol. Exp. Ther.* **1941**, *72*, 74.
(16) Howes, J. F.; Harris, L. S.; Dewey, W. L.; Voyda, C. A. *J. Pharmacol. Exp. Ther.* **1969**, *169*, 23.
(17) Litchfield, J. T., Jr.; Wilcoxon, F. *J. Pharmacol. Exp. Ther.* **1949**, *96*, 99.

Table I. Calculated Energy Conformational Profile for β-Meperidine Analogues



13a: R = CH_3; R′ = H
14a: R = H; R′ = H
15a: R = H; R′ = CH_3

analogue	3-Ph	2-R	3-$COOC_2H_5$	τ_1,[a] deg	τ_2,[b] deg	ΔE, kcal/mol
14a	eq	H	ax	176	128	2.1
	eq	H	ax	176	−64	0.4
	eq	H	ax	113	181	0.0
	ax	H	eq	193	−65	1.7
	ax	H	eq	64	122	3.4
	ax	H	eq	67	181	4.1
13a	eq	CH_3(ax)	ax	121	37	3.4
	eq	CH_3(ax)	ax	117	32	3.1
	eq	CH_3(ax)	ax	115	182	0.0
	ax	CH_3(eq)	eq	179	−84	5.0
	ax	CH_3(eq)	eq	168	101	5.5
15a	eq	CH_3(eq)	ax	82	−87	3.5
	eq	CH_3(eq)	ax	81	94	1.3
	eq	CH_3(eq)	ax	104	186	0.0
	ax	CH_3(ax)	eq	168	−68	2.4
	ax	CH_3(ax)	eq	171	109	4.2

[a] $\tau_1 = \tau C_8C_7C_3C_2$. [b] $\tau_2 = \tau O_{15}C_{13}C_3C_2$; $\tau_3 = C_{16}O_{15}C_{13}C_3 = 180°$ for all conformers; $\tau_4 = C_{17}C_{16}O_{15}C_{13} = 180°$ for all conformers.

(sc) of morphine sulfate caudal to the site of the first injection. They were tested 10, 20, 30, 45, and 60 min after treatment. Percent agonism at the time of peak effect of each dose was computed. Then percent antagonism was calculated for each dose level by applying the following formula:[18]

$$\% \text{ antagonism} = 100 - \frac{\% \text{ agonism of (test compound + morphine)}}{0.80}$$

From a plot of percent antagonism versus the log dose, the median effective antagonism dose (AD_{50}) and 95% confidence limits were determined.[17]

4. Theoretical Methods. All theoretical data reported in this study are based on molecular mechanics calculations using the program MOLMEC.[19] The geometries have been subject to a complete optimization of all variables. The partial charges for the Coulomb term were taken from MNDO[20] calculations using geometries, which were optimized by MOLMEC without the charge term.

Calculations have been performed for compounds **14a**, **13a**, **15a** (Table I) with the piperidine ring kept in a chair conformation and the nitrogen atom protonated. For all three compounds, optimized geometries and energies have been determined for conformations with the phenyl group in an equatorial and axial position. The search for conformational minima included rotations of the phenyl ring and ester group, i.e. optimization of τ_1–τ_4. Rotation of the phenyl ring, τ_1, by 180° resulted in a second conformation of equal energy to that reported for all analogues studied. Comparisons of the low-energy conformers of **13a** with metazocine were made by optimizing the overlap of designated pairs of atoms in two compounds. The root mean square (rms) deviation from total superposition is a measure of the extent of overlap.

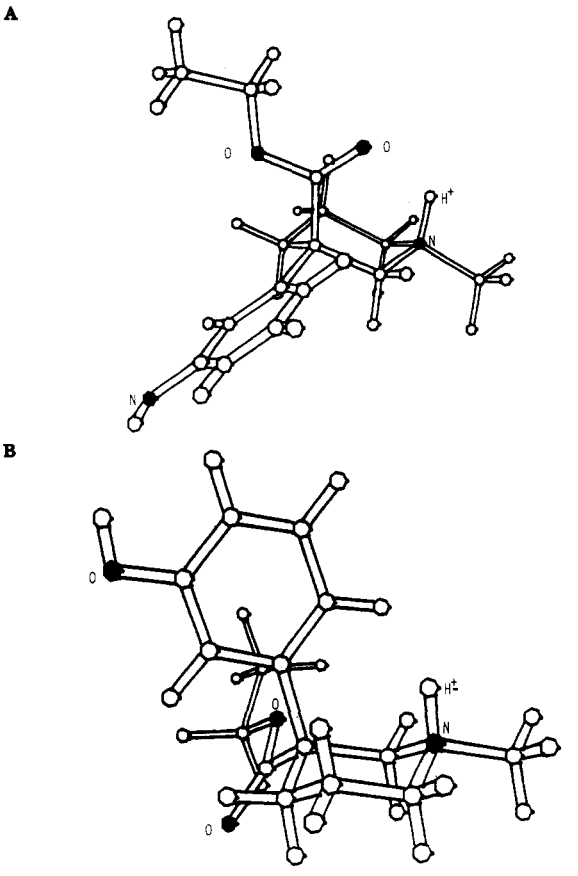


Figure 1. Lowest energy optimized conformers for analogue **14a** with (A) phenyl equatorial and (B) phenyl axial substituent. Lowest energy optimized conformers for analogue **13a** and **15a** are identical.

Results

The results of the energy-conformational calculations for the 3PPs are summarized in Table I. The parent des-2-methyl-β-meperidine structure **14a** has three low-energy phenyl equatorial conformers, with two of essen-

(18) Harris, L. S.; Pierson, A. K. *J. Pharmacol. Exp. Ther.* **1964**, *143*, 141.
(19) Oie, T.; Maggiora, G. M.; Christoffersen, R. E.; Duchamp, C. *Int. J. Quant. Chem.* **1981**, QBS *8*, 1.
(20) Dewar, M. J. S.; Thiel, W. J. *J. Am. Chem. Soc.* **1977**, *99*, 4899.

Table II. Receptor Binding Affinities of β-Meperidine Analogues (K_D, nM[a])

analogue	μ^a	δ^a	κ^b
DADL	7.7 ± 0.6	1.0 ± 0.2	
EKC	1.1 ± 0.1	16.1 ± 1.6	
DSLET	21.7 ± 2.0	0.7 ± 0.1	
DHM	1.8 ± 0.2	111 ± 11	
U69,593			4.3 ± 0.72
14a	36 ± 12	4000 ± 700	2200 ± 540
14b	26 ± 7	715 ± 120	450 ± 92
14c	8 ± 2	260 ± 46	120 ± 23
13a	178 ± 21	910 ± 91	1900 ± 520
13b	310 ± 36	770 ± 78	830 ± 190
13c	154 ± 15	625 ± 60	830 ± 180
13d	380 ± 42	170 ± 29	2600 ± 560

[a] Affinities at μ and δ were obtained from the computer analysis of the binding data in rat brain membranes with LIGAND, as described in Methods. [b] Affinities at κ were obtained from the computer analysis of the inhibition of [^{3}H]U69,593 by each compound in guinea pig brain membranes as described in Methods.

tially equal energy involving trans 3-ester (τ_1 ~180) and trans 3-phenyl (τ_2 ~180) orientations. The very lowest phenyl equatorial conformer shown in Figure 1A is preferred by 1.7 kcal/mol over the best phenyl axial conformer (Figure 1B). Two additional conformational minima were found for the phenyl group in the axial position but with increased energy separation between them as shown in Table I. The preference of a phenyl equatorial to a phenyl axial conformer is similar to that found for meperidine itself.

Surprisingly, addition of a CH_3 to the 2-position, either cis (**13a**), or trans (**15a**), to the *m*-hydroxyphenyl group failed to produce a phenyl axial preferred conformer. A priori, one might have expected that analogue **13a**, formed by the addition of a *cis*-2-methyl to analogue **14a**, would prefer a 3-phenyl axial conformer instead of a phenyl equatorial conformer that has both an axial 2-methyl and an axial 3-CO_2Et group. Apparently, however, any destablizing interactions of these axial groups are more than balanced by repulsive interactions that occur in the axial phenyl conformer between the phenyl group and axial hydrogen atoms at N_1 and C_4, resulting in a higher energy conformer. Similar steric hindrance for the phenyl axial conformer of analogue **15a** was found. The most favorable phenyl axial conformers for the these analogues are higher in energy than the preferred phenyl equatorial conformer by 5.0 kcal/mol for **13a** and 2.4 kcal/mol for **15a**, compared to 1.7 kcal/mol for **14a**. For both configurations of the 2-methyl group, **13a** and **15a**, the preferred phenyl equatorial conformer has torsion angles very similar to the parent **14a** with 2R = H, and the energy separation among the phenyl equatorial conformers of **13a** and **15a** is somewhat increased (Table I). Thus, the addition of a 2-methyl to the parent compound, either cis or trans to the 3-phenyl group, does not produce a significant conformational change in the β-meperidines. These theoretical results are confirmed by our NMR studies on **13a** and **14a**, as described above. The ^{1}H NMR spectra of **13a** and **14a** are quite similar to each other and are consistent with both existing in a phenyl equatorial conformer.

Table II summarizes the receptor binding affinity data for both the parent (des-2-methyl) analogues, **14a–c**, and the newly synthesized 2-methyl analogues **13a–d**. Comparison of the results for **13a–c** and **14a–c** indicates that the introduction of a 2-methyl group cis to the 3-phenyl group reduces the affinity of each analogue at μ-receptors while having less effect on binding to δ or κ. Thus, the 2-methyl analogues (**13a–c**) have lower affinity and are less μ-selective than the parent analogues (**14a–c**).

Table III. Narcotic Analgesic and Antagonist Potencies of β-Meperidines with N-Substituent Variations Evaluated in the Mouse Tail-Flick Test

analogue	analogue substitutions	agonism: ED_{50} (95% CL), μmol/kg (sc)	antagonism:[a] AD_{50} (95% CL), μmol/kg (sc)
(NCH_3)			
13a	$R^2 = CH_3$[b]	>510 (38.3%)[d]	14 (4.8–42.9)
14a	$R^2 = H$[c]	>290	24 (6.1–84.4)
($NCH_2CH{=}CH_2$)			
13b	$R^2 = CH_3$[b]	>118 (17.4%)[d]	112 (51.1–247.5)
14b	$R^2 = H$[c]	>229[c]	>192[c]
($NCH_2C_3H_5$)			
13c	$R^2 = CH_3$[b]	>452 (43.3%)[d]	75 (38.1–149.5)
14c	$R^2 = H$[c]	68 (34–76)	19 (4.9–71.5)
(NCH_2CH_2Ph)			
13d	$R^2 = CH_3$[b]	>198 (46.5%)[d]	>198 (24.2%)[d]
14d	R = H		
meperidine		25 (14.2–43.2)	no antagonism
nalorphine		828.0 (55–1250)	2 (1.4–2.9)

[a] Antagonism of mouse tail-flick inhibition induced by 21.08 μmol/kg morphine (sc). [b] These are racemic mixtures of (±) α-(2-CH_3-3φcis) isomers. [c] Data from ref 4. No percentage activity given for higher dose in that reference. [d] Percent agonism, antagonism at highest dose evaluated.

Table III summarizes our pharmacological evaluation of the new analogues **13a–d** and, for comparison, also gives the literature values previously reported[4] for **14a–c**. No significant agonism was found for any of the 2-methyl analogs. As shown in Table III, this behavior is similar to that previously reported for their des-methyl counterparts **14a–c**. Except for the N-CPM analogue, **14c**, which was found to have modest agonist activity, the des-2-CH_3 analogues had only antagonist activity. Of the four 2-CH_3 analogues studied, **13a–c** were found to have moderate to weak antagonist potencies 2–14% that of nalorphine while the *N*-phenethyl analogue had only 24% activity at the highest dose.

Discussion

In the 4-alkyl, 4-(*m*-hydroxyphenyl)piperidine (4PP) opiate family, it has been shown that the introduction of an axial 3-methyl group to the carbon adjacent to a 4-*m*-hydroxyphenyl group reduces the efficacy of the parent, leading to high affinity pure potent antagonists.[6] The effect of addition of an axial β-3-methyl in the prodine (4-propionyl) family is less clear since *m*-hydroxy-β-prodine has been described as a weak antagonist in mice[6] and in a different study,[21] as inactive both as an agonist or antagonist in rats. Previous theoretical investigation of 4PPs[22] have determined that one effect of the introduction of an axial 3-methyl in desmethylprodines is to stabilize the phenyl equatorial conformer.

This study examines, in an analogous manner, the effect of introduction of an axial methyl to the carbon atom adjacent to the phenyl substituent in a family of 3PPs with an ester group. As shown in Table I, comparing **14a** and **13a**, the effect on conformation is to stabilize the lowest energy phenyl equatorial conformer while leaving the torsion angles virtually unchanged. The receptor binding results suggest that, where direct comparisons are possible, **13a–c** vs **14a–c**, affinities at μ are significantly lowered by addition of the 2-methyl moiety, while affinities at δ and κ remain relatively unchanged. Given the similarity of conformation, the decrease in μ-affinity is most likely due

(21) Casy, A. F.; Ogungbamila, F. O. *J. Pharm. Pharmacol.* **1985**, *37*, 121.
(22) Loew, G. H.; Burt, S. K.; Hashimoto, G. M. Proceedings of the 42nd Annual Meeting Committee on Problems of Drug Dependence; 1980, p 399.

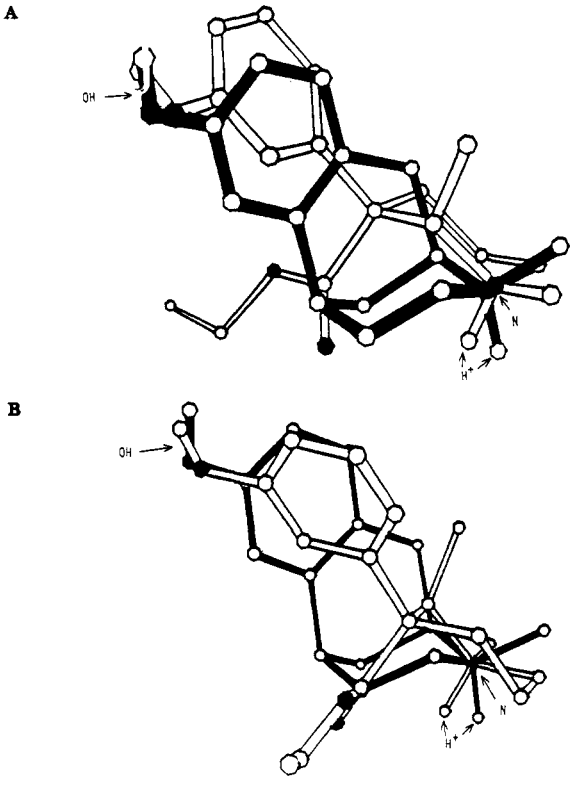


Figure 2. Postulated mode of receptor binding (pharmacophore) of enantiomers of 3-phenylpiperidines leading to antagonist activity. These pharmacophores are superimposed with optimum overlap of the *m*-OH and protonated amine group (NH) on a benzomorphan fused ring skeleton shown in black. (A) Overlap of 2*S*,3*S* isomer of **13a** has a root mean square of 0.373. (B) Overlap of 2*R*,3*R* isomer of **13a** has a root mean square of 0.376 for these four atoms.

to unfavorable steric interactions of the axial 2-methyl group, itself, with the μ-receptor, which do not appear to be present in the δ- or κ-receptor.

As shown in Table I, our calculations indicate that the other diastereomers of **13a–d**, epimeric at C-2, (**15a–d**), will also be in a phenyl equatorial conformer with the most preferred conformer of **13a** and **15a** having similar torsion angles. Thus, the major difference between the unknown epimers **15a–d** and those studied, **13a–d**, is that the 2-methyl is equatorial instead of axial. While it is possible that **15a–d** could have improved affinities, should the equatorial methyl group find a more favorable binding site, the generally low affinities and activities of both the des-2-methyl and axial 2-methyl analogues are not encouraging enough to warrent further investigation.

Not only do we predict similar pharmacological profiles for the epimers of **13a–d**, our results also suggest that both enantiomers of **13a**, 2*S*,3*S* and 2*R*,3*R* will have similar behavior.

Shown in Figure 2 is a proposed mode of binding (i.e., a pharmacophore) of the two enantiomers of **13a**, 2*S*,3*S* (Figure 2A) and 2*R*,3*R* (Figure 2B) relative to metazocine, used as a template for a relatively nonselective, high-affinity ligand. In these figures, the *m*-hydroxyphenyl group and the protonated amine NH group of **13a** are superimposed on the same groups in metazocine, implying similar contact with receptor subsites. It is apparent from these figures and the RMS values (<0.38) for optimum overlap of these four atoms that it is possible to closely overlap the NH and OH groups of both enantiomers of **13a** and benzomorphan. These results, taken together with the observation of nearly pure antagonism for the racemate of **13a**, strongly suggest that both enantiomers of **13a–c** are behaving similarly, although it is always possible that weak agonism of one enantiomer could be masked in the racemates.

In the series studied, the N–CH_3 analogue, **13a**, is the most potent antagonist and the *N*-phenethyl analogue, **13d**, is the one with lowest affinity. These results clearly indicate that N-substituent variations do not affect affinities or activities as in fused-ring families of opiates such as morphine or benzomorphans.

Figure 2 provides some insight into reasons why NR variations produce different results in these two families. While the crucial overlaps of the NH and OH portions of both enantiomers of **13a** with those of metazocine are possible; it is also clear that neither the phenyl groups nor the piperidine rings have similar orientations. Moreover, the relative orientation of the N-substituent in the two families is significantly different. These displacements may prevent optimum interaction with the opiate receptor, accounting for both diminished receptor affinity and could also explain the very different N-substituent modulation of affinity and agonist/antagonist activity observed in these analogues compared to fused-ring opioids.

Experimental Section

All reactions were performed under a nitrogen or argon atmosphere, and solvents were removed on a rotary evaporator under vacuum. Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. NMR spectra were recorded on Varian EM360, 390, XL400 or JOEL FX90 instruments. Chemical shift values are reported in parts per million (δ) relative to Me_4Si. MS were determined on a LKB 9000 spectrometer equipped with a gas chromatograph and a PDP12 computer. Analytical HPLC was carried out on a Waters Radialpak column, and preparative liquid chromatography was performed on a Waters Prep LC/500 system. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN, and are within ±0.4% of theoretical values.

Ethyl 2-(*m*-Methoxyphenyl)-3-hydroxybutanoate (3). To a mixture of ethyl *m*-methoxyphenylacetate (**2**) (37.2 g, 193 mmol) and acetaldehyde (9.7 mL, 220 mmol) in 150 mL of DMSO was added sodium ethoxide (37.4 mL of a 0.5 N solution freshly prepared from 0.47 g of sodium and 40 mL of absolute EtOH) dropwise over a period of 1 h at room temperature (rt). After 2 h, the reaction was quenched with glacial acetic acid and worked up to yield 41 g of crude oil. The oil was chromatographed on a silica gel column (preparative HPLC) and eluted initially with CH_2Cl_2 and finally with a mixture of EtOAc–CH_2Cl_2 (5:95). The desired fractions (analytical HPLC) were pooled, and solvent was evaporated under vacuum to leave 27.8 g (61%) of **3**, a yellowish oil: NMR ($CDCl_3$) δ 6.73–7.40 (m, 4 H, Ar H), 3.93–4.50 (m, 3 H, CH_2CH_3, $CHCH_3$), 3.83 (s, 3 H, OCH_3), 3.43 (d, 1 H, CH), 2.55 (br s, 1 H, OH), 0.93–1.42 (m, 6 H, CH_2CH_3, $CHCH_3$).

Ethyl 2-(*m*-Methoxyphenyl)-2-butanoate (4). A mixture of **3** (23.7 g, 99.6 mmol), phosphorus oxychloride (15 mL, 94 mmol), and 130 mL of pyridine was heated at 80 °C for 6 h. The solvent was concentrated under vacuum, and 300 mL of $CHCl_3$ was added to the residue. The mixture was washed with dilute HCl and H_2O, dried, and filtered through a silica gel column (CH_2Cl_2). The eluent was concentrated to yield 19.7 g (90%) of **4**, an oil. ^1H NMR revealed a 30:70 ratio of *cis*-methyl to *trans*-methyl material: NMR ($CDCl_3$) δ 6.67–7.50 (m, 4.7 H, arom CH=C), 6.28 (q, 0.3 H, CH=C), 4.30 (q, 2 H, CH_2CH_3), 2.00 (d, 0.9 H, CH_3C=C), 1.73 (d, 2.1 H, CH_3C=C), 1.23 (t, 3 H, CH_2CH_3).

Ethyl 2-(*m*-Methoxyphenyl)-3-[(3′-hydroxypropyl)-amino]butanoate (5). Ethyl butenoate **4** (20 g, 90.9 mmol) was treated with a solution of 3-aminopropanol (8.4 mL, 110 mmol) in 10 mL of absolute EtOH. The reaction mixture was allowed to stand at rt for 7 days. The reaction mixture was diluted with CH_2Cl_2 and extracted with 3 N HCl solution to remove the product **5** from unreacted **4**. The organic layer yield 3.5 g of **4**, and the aqueous layer was made basic with solid K_2CO_3 and extracted with $CHCl_3$ (3 × 150 mL). The organic extracts were dried (Na_2SO_4) and concentrated in vacuo to give 15.7 g (71%), based on recovered **4**, or **5**: NMR ($CDCl_3$) δ 6.67–7.50 (m, 4 H, arom),

Table IV. Physical Data on Ethyl α-2-Methylnipecotates

compd	R	X[a]	yield,[b] %	mp, °C	empirical formula[c]
(±)-13a	CH_3	picrate	52	199–200	$C_{16}H_{23}NO_3 \cdot C_6H_3N_3O_7$
(±)-13b	allyl	Cl	61	155–157	$C_{18}H_{25}NO_3 \cdot HCl$
(±)-13c	CPM	Cl	63	128–130	$C_{19}H_{27}NO_3 \cdot HCl$
(±)-13d	phenethyl	Cl	69	123–125	$C_{23}H_{29}NO_3 \cdot HCl$

[a] Counterion. [b] From 11. [c] Analyses for C, H, N ±0.4% theory.

4.15 (q, 2 H, CH_2CH_3), 3.80 (s, 3 H, OCH_3), 3.27–3.90 (m, 4 H, $NHCH_2$, CHNH, CHCOOEt), 2.10–3.27 (m, 2 H, CH_2OH), 1.37–2.00 (m, 2 H, CH_2CH_2OH), 0.70–1.37 (m, 6 H, CH_3, CH_2CH_3).

Ethyl 2-(*m*-Methoxyphenyl)-3-[*N*-formyl-*N*-[3′-(formyloxy)propyl]amino]butanoate (6). To amine **5** (15.7 g, 53.2 mmol) was added a mixture of formic acid (98–100%, 85 mL, 1.8 mmol) and acetic anhydride (28 mL, 274 mmol). The reaction mixture was stirred for 1.5 h at 70 °C. The solvent was removed under vacuum, 100 mL of H_2O was added, and the mixture was extracted with two 100-mL portions of $CHCl_3$. After being washed with saturated $NaHCO_3$ solution (3 × 50 mL) and H_2O (2 × 50 mL), the extract was dried ($MgSO_4$) and concentrated under vacuum to provide 15.4 g (82%) of **6**, a colorless liquid: NMR ($CDCl_3$) δ 8.33 (s, 0.5 H, NCHO), 8.17 (s, 1 H, OCHO), 7.90 (s, 0.5 H, NCHO), 6.70–7.40 (m, 4 H, arom), 3.70–4.67 (m, 7 H, CH_2CH_3, CH_2OCHO, CH_2NCHO, CHNCHO), 3.83 (s, OCH_3), 3.77 (s, OCH_3), 2.65–3.65 (m, 3 H, NCH_2, Ar CH), 1.55–2.20 (m, 2 H, NCH_2CH_2), 0.90–1.50 (m, 6 H, CH_3).

Ethyl 2-(*m*-Methoxyphenyl)-3-[*N*-formyl-*N*-(3′-hydroxypropyl)amino]butanoate (7). To a solution of **6** (15.4 g, 43.9 mmol) in 65 mL of methanol was added a solution of $KHCO_3$ (4.7 g, 51.1 mmol) in 55 mL of H_2O. The resulting mixture was allowed to stir for 16 h at rt. The solvent was evaporated, and workup gave 14.0 g (98%) of **7**, a colorless oil: NMR ($CDCl_3$) δ 8.30 (s, 0.5 H, NCHO), 7.87 (s, 0.5 H, NCHO), 6.60–7.43 (m, 4 H, arom), 3.70–4.60 (m, 2 H, CH_2CH_3), 3.80 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 3.00–3.70 (m, 6 H, CH_2OH, CHN, CH_2N, CHPh), 1.50–2.0 (m, 2 H, NCH_2CH_2), 0.90–1.50 (m, 6 H, CH_3, CH_2CH_3).

Ethyl 2-(*m*-Methoxyphenyl)-3-[*N*-formyl-*N*-(3′-mesyloxypropyl)amino]butanoate (8). A solution of **7** (14 g, 43.3 mmol) in 120 mL of pyridine (distilled from BaO) was cooled in an ice bath, and then methanesulfonyl chloride (3.9 mL, 50 mmol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 2 h and was then poured into 300 mL of ice water. Workup afforded 17 g (98%) of **8**, a yellow oil: NMR ($CDCl_3$) δ 8.26 (s, CHO), 7.85 (s, CHO), 6.75–7.40 (m, 4 H, arom), 3.90–4.45 (m, 4 H, NCH_2, $COOCH_2CH_3$), 3.80 (s, OCH_3), 3.76 (s, OCH_3), 2.80–3.75 (m, 2 H, NCH, Ar CH), 3.10 (s, SO_2CH_3), 3.00 (s, SO_2CH_3), 1.50–2.20 (m, 2 H, NCH_2CH_2), 0.90–1.40 (m, 6 H, $COOCH_2CH_3$, $CHCH_3$).

Ethyl 2-(*m*-Methoxyphenyl)-3-[*N*-formyl-*N*-(3′-iodopropyl)amino]butanoate (9). To mesylate **8** (17 g, 42.4 mmol) was added a 10% solution of sodium iodide (13 g, 86.7 mmol) in acetone (distilled). The reaction mixture was allowed to stir for 5 h at rt during which time a white precipitate appeared. Standard workup yielded 12.3 g (67%) of **9**, a yellow oil: NMR ($CDCl_3$) δ 8.30 (s, CHO), 7.90 (s, CHO), 6.75–7.50 (m, 4 H, arom), 3.90–4.50 (m, 4 H, NCH_2, $COOCH_2$), 3.83 (s, OCH_3), 3.87 (s, OCH_3), 1.50–3.50 (m, 5 H, Ar CH, NCH_2CH_2, CH_2I), 0.90–1.40 (m, 6 H, $COOCH_2CH_3$, Ar $CHCHCH_3$).

1-Formyl-2-methyl-3-(ethoxycarbonyl)-3-(*m*-methoxyphenyl)piperidine (10). To a dry three-neck flask was added potassium hydride (35% in mineral oil, 1.7 g, 14.8 mmol) and 50 mL of DMF (distilled). The suspension was cooled in a salt–ice bath, and iodo compound **9** (6.3 g, 14.6 mmol) in 30 mL of dry DMF was added dropwise with stirring over a period of 1 h. The mixture was stirred for an additional 8 h at 0 °C and for 16 h at rt. The reaction was quenched with 50 mL of water and worked up to give an oily residue, which was HPLC (silica gel), eluting with CH_2Cl_2 and then 5% EtOAc–CH_2Cl_2, which gave 1.3 g (30%) of **10**: NMR ($CDCl_3$) δ 8.19 (s, 0.3 H, CHO), 7.96 (s, 0.7 H, CHO), 6.55–7.40 (m, 4 H, arom), 5.53 (q, 0.7 H, $CHCH_3$), 4.57 (q, 0.3 H, $CHCH_3$), 4.06 (m, 2 H, CH_2CH_3), 3.77 (s, 3 H, OCH_3), 3.25 (m, 2 H, CH_2N), 2.35 (m, 2 H, CH_2), 1.22 (m, 8 H, $CHCH_3$, CH_2CH_3, CH_2).

2-Methyl-3-(ethoxycarbonyl)-3-(*m*-methoxyphenyl)piperidine (11). *N*-formylpiperidine **10** (3.94 g, 12.9 mmol) in 30 mL of a 9% ethanolic HCl solution was stirred at reflux for 24 h. After cooling, the solvent was removed under reduced pressure, the residue in 30 mL of dilute HCl solution was washed with Et_2O, neutralized with NaOH, and extracted into Et_2O to give 2.64 g (74%) of 11α,β: NMR on 11α ($CDCl_3$) δ 6.60–7.25 (m, 4 H, arom), 4.21 (q, 2 H, CH_2), 3.80 (s, 3 H, OCH_3), 1.80–3.27 (m, 5 H, $CHCH_3$, CH_2NH, CH_2), 1.95 (s, 1 H, NH), 1.40–1.80 (m, 2 H, CH_2), 1.27 (t, 3 H, OCH_2CH_3), 1.15 [d, 2.7 H, $CHCH_3$ (major)], 0.82 [d, 0.3 H, $CHCH_3$ (minor)]. The analytical sample (HCl salt from ether) was crystallized from 2-propanol ether to give 11α·HCl, a white solid: mp 158–160 °C. Anal. ($C_{16}H_{24}NO_3Cl$) C, H, N, Cl.

General Methods to N-Alkylate 11a and O-Demethylate 12a–d. Compound **11a** was N-alkylated in two ways. The NCH_3 derivative **12a** was prepared by using the Borch N-alkylation procedure we have previously described.[4] The *N*-allyl, -CPM, and phenethyl analogues **12b–d** were prepared from the alkyl halide in the presence of $KHCO_3$, and the resulting ether then O-demethylated with BBr_3, as also previously described.[4] Physical properties of (±)-**13a–d** are in Table IV.

NMR ($CDCl_3$) for (±)-13a–d. ^1H spectra, (±)-13a: δ 1.06 (d, J = 6.8 Hz, 3 H, CH_3), 1.11 (t, J = 6.4 Hz, 3 H, CH_3), 1.45–1.55 (m, 2 H, C-5 CH_2), 2.0–2.25 (m, 2 H, C-4, CH_2), 2.35 (s, 3 H, NCH_3) 2.35–2.55 (m, 2 H, C-6 CH_2), 3.52 (q, J = 6.5 Hz, 1 H, $CHCH_3$), 4.03 (m, 2 H, OCH_2), 6.57 (d, 1 H, arom), 6.8 (d, 1 H, 4′-arom), 6.9 (s, 1 H, 2′-arom), 7.1 (t, 1 H, 5′-arom), 7.2 (s, 1 H, OH).

(±)-13b: δ 1.0 (d, 3 H, CH_3), 1.1 (t, 3 H, CH_3CH_2), 1.2–2.6 (m, 6 H, $(CH_2)_3$), 3.15 (d, 2 H, NCH_2CHCH_2), 3.8 (q, 1 H, $CHCH_3$), 4.05 (q, 2 H, OCH_2), 5.0–6.3 (m, 3 H, $CH{=}CH_2$), 6.4–7.4 (m, 4 H, arom).

(±)-13c: δ 0.15 (m, 2 H, cyclopropyl), 0.55 (m, 2 H, cyclopropyl), 0.93 (m, 1 H, cyclopropyl), 0.94 (d, 3 H, $CHCH_3$) 1.10 (t, 3 H, CH_3CH_2), 1.3–1.4 (m, 2 H, C-5 CH_2), 1.65 (br peak, 1 H, OH), 2.1, 2.35, 2.6 (m, 4 H, C-4, C-6-CH_2), 2.20, 2.48 (d of d, J_{gem} = 13 Hz, J_{ab} = 7 Hz, 2 H, CH_2-cyclopropyl), 4.00 (q, 1 H, $CHCH_3$), 4.01, 4.05 (d of q, J_{gem} = 12 Hz, J_{ab} = 7 Hz, 2 H, $-OCH_2CH_3$), 6.6 (d, 1 H, C-4′ arom), 6.9–7.1 (m, 3 H, arom).

(±)-13d: δ 1.0 (d, 3 H, CH_3CH), δ 1.1 (t, 3 H, CH_3CH_2), 1.2–2.7 (m, 6 H, $(CH_2)_3$) 2.80 (s, 4 H, NCH_2CH_2Ph), 3.80 (q, 1 H, CH_3CH), 4.05 (q, 2 H, OCH_2CH_3), 5.3 (br s, 1 H, OH), 6.7 (d, 1 H, C-4′ arom), 6.8–7.2 (m, 3 H, arom), 7.30 (s, 5 H, phenyl).

^{13}C Assignments for 13a (ppm), in $CDCl_3$: 2 CH_3, 7.5; OCH_2CH_3, 13.9; C-5, 21.4; C-4, 27.3; NCH_3, 43.1; C-6, 48.7; C-3, 54.4; C-2, 58.6; OCH_2, 60.7; 6′-arom, 113.9; 4′(or 2′)-arom, 114.7; 2′(or 4′)-arom, 119.1; 5′-arom, 129.3; 1′-arom, 142.8; 3′-arom, 156.2; carbonyl, 174.5.

Acknowledgment. Support for this work from the National Institute on Drug Abuse, Grant DA02622, is gratefully acknowledged.

Registry No. 1, 1798-09-0; **2**, 35553-92-5; **3**, 115981-89-0; (*Z*)-4, 115981-90-3; (*E*)-4, 115981-91-4; **5**, 115981-92-5; **6**, 115981-93-6; **7**, 115981-94-7; **8**, 115981-95-8; **9**, 115981-96-9; **10**α, 115981-97-0; **10**β, 115981-98-1; 11α (free base), 115981-99-2; 11α·HCl, 115982-00-8; 11β (free base), 115982-01-9; **12a**, 115982-02-0; **12b**, 115982-03-1; **12c**, 115982-04-2; **12d**, 115982-05-3; **13a**, 115982-06-4; **13a** (free base), 115982-07-5; **13a** (picrate), 115982-08-6; **13b**, 115982-09-7; **13b** (free base), 115982-10-0; **13c**, 115982-11-1; **13c** (free base), 115982-12-2; **13d**, 115982-13-3; **13d** (free base), 115982-14-4; **14a**, 115982-15-5; **14b**, 115982-16-6; **14c**, 115982-17-7; **15a**, 115982-18-8; $NH_2(CH_2)_3OH$, 156-87-6.