Synthesis and Spectral Analysis of (±)-*cis*-*N*-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide and (±)-*cis*-*N*-[1-(2-Hydroxy-1-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide

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Treatment of (±)-*cis*-*N*-(3-methyl-4-piperidyl)-*N*-phenylpropanamide (**2**) with styrene oxide (**1**) yielded a mixture of (±)-*cis*-*N*-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**3**) and (±)-*cis*-*N*-[1-(2-hydroxy-1-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**4**). The structure of compound **3** was confirmed by an unambiguous synthesis *via* (±)-*cis*-*N*-[1-(2-oxo-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**6**). The proton and carbon-13 resonances of compounds **3** and **4** were assigned with the aid of two-dimensional heteronuclear correlation experiments.

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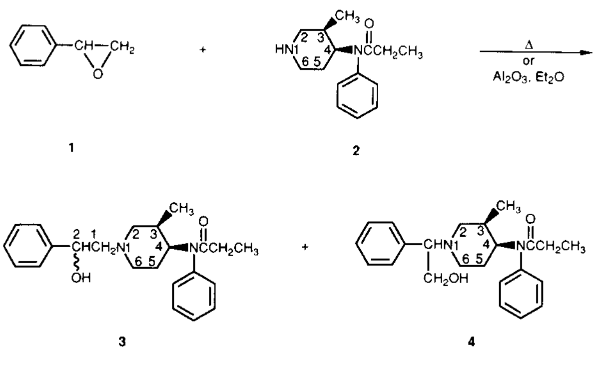
(±)-*cis*-*N*-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**3**) is an extremely interesting addition to the 4-anilidopiperidine class of analgesics. For example, test results from monkeys have shown that compound **3** is approximately 25,000 times more potent than morphine [1], which puts it into the same potency level as carfentanil. In addition, *in vitro* ligand binding studies have shown that the same compound has a 27,000-fold binding selectivity for *mu versus delta* opioid receptors [2].

Our initial synthesis of (±)-*cis*-*N*-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**3**) involved heating a neat mixture of (±)-*cis*-*N*-(3-methyl-4-piperidyl)-*N*-phenylpropanamide (**2**) [3] with styrene oxide (**1**) [2] (*cf.* Scheme I). This procedure, which was based on a reported preparation of (±)-*N*-[1-(2-hydroxy-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (*β*-hydroxyfentanyl) [4], generated a mixture from which the desired product **3** was isolated by chromatography. We also isolated a minor by-product which we determined to be the isomeric compound (±)-*cis*-*N*-[1-(2-hydroxy-1-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**4**). The formation of compound **4** resulted from nucleophilic attack at the benzylic carbon of styrene oxide (**1**) by (±)-*cis*-*N*-(3-methyl-4-piperidyl)-*N*-phenylpropanamide (**2**).

Scheme I

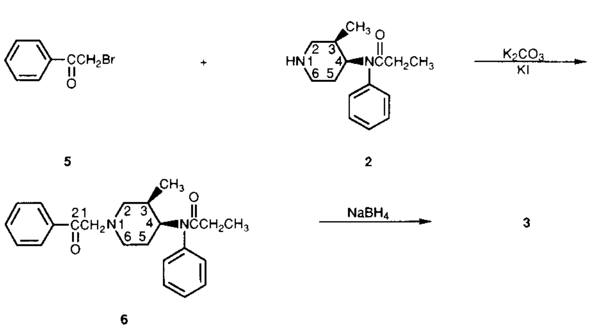


(Only one of the two possible cis arrangements of the piperidine C-3 and C-4 substituents is shown.)

Subsequently we repeated the styrene oxide synthesis using a modified procedure in which the reaction was carried out in diethyl ether solution at room temperature in the presence of neutral alumina [5]. This procedure, which was cleaner than the initial approach, also afforded a mixture of compounds **3** and **4**. However, in this case, the isolated quantity of compound **4** (free base) was slightly greater than that of compound **3**. This result was consistent with the regiospecificity observed in the opening of indene oxide in the presence of neutral alumina [5]. We used this modified procedure to prepare sufficient amounts of compound **4** for biological testing.

The structure of compound **3** was confirmed by preparing it using an unambiguous route [6,7]. Thus, alkylation of (±)-*cis*-*N*-(3-methyl-4-piperidyl)-*N*-phenylpropanamide (**2**) with 2-bromoacetophenone (**5**) afforded (±)-*cis*-*N*-[1-(2-oxo-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**6**) (*cf.* Scheme II). Subsequent sodium borohydride reduction of ketone **6** yielded compound **3** which was chromatographically and spectroscopically identical to the material synthesized using the styrene oxide procedures. Interestingly, our purified sample of compound **3** derived from ketone **6** was a mixture of the four possible isomers (two diastereoisomeric pairs) whereas the reported product [7] was a mixture of the two less soluble isomers (one diastereoisomeric pair) [8].

Scheme II

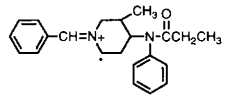
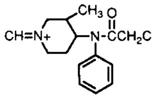
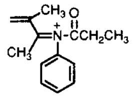
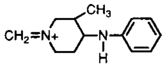
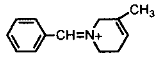
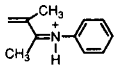
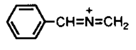


(Only one of the two possible cis arrangements of the piperidine C-3 and C-4 substituents is shown.)

Mass spectral analysis of compounds **3** and **4** gave the results summarized in Table I. Although no molecular ion was observed, the four major fragment ions seen in the spectrum of compound **3** were identical to the ions observed in the electron-impact mass spectrum of *cis*-3-methylfentanyl [9]. This result emphasized the structural similarity between compound **3** and *cis*-3-methylfentanyl. In contrast, the mass spectrum of compound **4** contained some significant differences, the most notable of which was the intense ion at m/z 334. As shown in Table I, we postulated the radical ion formed by loss of methanol from the parent structure, the loss being accompanied by abstraction of a proton. The ions at m/z 259 and m/z 203 were absent from the spectrum of compound **4**, while new ions were observed at m/z 186 and m/z 118. The similarities to the mass spectrum of compound **3** included the absence of a molecular ion and the presence of ions at m/z 216 and m/z 160. The presence of these latter ions indicated that the two compounds had identical substituents at the piperidine 3- and 4-positions. We concluded from the mass spectral analysis that compounds **3** and **4** differed from each other only in the piperidine 1-substituents (the phenylethyl portions of the molecules). This conclusion was supported by the formation of both compounds in the synthetic route involving styrene oxide.

Table I

Postulated Structures of Major EI-MS Ions [a]

Ion	Relative Intensity	
	3	4
 m/z 334	---	100
 m/z 259	100	---
 m/z 216	21	13
 m/z 203	46	---
 m/z 186	---	11
 m/z 160	46	21
 m/z 118	---	32

[a] The compounds were analyzed as the hydrochloride salts.

Partial carbon-13 and proton nmr data on compounds **3** and **4** are summarized in Tables II and III, respectively. The data are organized so that the proton signals are listed beside the carbon-13 signals to which they were correlated by the two-dimensional heteronuclear correlation experiments. Thus, in Table II, the three-proton triplet at δ 1.00 was correlated with the carbon-13 resonance at δ 9.28. The spectral data are consonant with a solution conformation (under the conditions of the nmr experiments) in which the piperidine ring is in a chair conformation, the bulky 1-(substituted phenylethyl) and 4-propionanilide substituents occupy equatorial positions, and the 3-methyl group *cis* to the piperidine 4-substituent is axial. The same solution conformation has been observed during proton nmr analyses of *cis*-3-methylfentanyl [9-11], the corresponding 1-benzyl analog [3b] and compound **2** [3b].

The data summarized in Table II for compound **3** were obtained on a sample synthesized using the styrene oxide approach. Essentially identical nmr data were obtained on a sample prepared by reduction of ketone **6**. The complexity of the spectra on both samples was due to the fact that the samples were mixtures of diastereoisomeric pairs [8]. In the carbon-13 spectra pairs of resonances were observed for both phenylethyl carbons and four of the piperidine carbons (C-2, C-3, C-5, C-6). The largest separation was between the C-2 and C-6 pairs. In the proton spectra three signals were present which integrated for half a proton and another multiplet was observed integrated for one and a half protons. The appearance and integration of the spectra suggested that the diastereoisomeric pairs were present in approximately equal amounts.

The proton nmr chemical shifts shown in Table II for the propanamide ethyl group and the *cis*-3-methyl group agreed well with values reported for the same groups in *cis*-3-methylfentanyl [9,10] and some related analogs [3b]. The appearance of the methylene signal as an apparent doublet of quartets instead of a quartet was attributed to a nonequivalence of the methylene protons due most likely to the proximity of the anilide aromatic ring. The upfield shift of a phenyl proton resonance, which was also observed in the proton nmr spectrum of compound **2**, was likewise indicative of a steric crowding effect. The correlation experiment confirmed the carbon-13 assignments for these groups. In the case of the propanamide ethyl group, the carbon-13 resonances were consistent with values previously observed for other fentanyl analogs containing the propanamide group [12].

The phenylethyl carbon resonances were in good agreement with the chemical shift values reported for the corresponding carbons of (±)-*N*-[1-(2-hydroxy-2-phenylethyl)-4-

Table II

Partial Carbon-13 and Proton NMR Correlations for Compound **3** [a,b]

Carbon-13		Proton				
Signal	Assignment	Signal				Assignment
9.28 (q)	$CH_2\mathbf{C}H_3$	1.00	t		3H	$CH_2C\mathbf{H}_3$
28.59 (t)	$\mathbf{C}H_2CH_3$	1.93	dq		2H	$C\mathbf{H}_2CH_3$
13.25 (q)	3-$\mathbf{C}H_3$	1.15	d	J = 7.1 Hz	3H	3-$C\mathbf{H}_3$
57.38 (t)	**C**-2	2.26-2.44 2.93	overlapping m d	 J = 11.4 Hz	3H 0.5H	2-**H**a 2-**H**e
61.20 (t)	**C**-2	2.56-2.73	overlapping m		1.5H	2-**H**e, 2-**H**a
30.76 (d) 31.44 (d)	**C**-3	2.78	m		1H	3-**H**e
56.90 (d)	**C**-4	4.44	dt		1H	4-**H**a
25.82 (t) 26.15 (t)	**C**-5	1.26-1.55	overlapping m		2H	5-**H**e, 5-**H**a
51.50 (t)	**C**-6	2.03 3.02	td d	 J = 11.2 Hz	0.5H 0.5H	6-**H**a 6-**H**e
55.14 (t)	**C**-6	2.26-2.44 2.56-2.73	overlapping m overlapping m		3H 1.5H	6-**H**a 6-**H**e
65.55 (t) 65.75 (t)	$CHOH\mathbf{C}H_2N$	2.26-2.44	overlapping m		3H	$CHOHC\mathbf{H}_2N$
68.38 (d) 68.72 (d)	$\mathbf{C}HOHCH_2N$	4.64	m		1H	$C\mathbf{H}OHCH_2N$

[a] Abbreviations: a = axial, e = equatorial, d = doublet, m = multiplet, q = quartet, t = triplet, dq = doublet of quartets, dt = doublet of triplets, td = triplet of doublets.

[b] This table includes the following overlapping multiplets observed in the proton nmr spectrum: δ 1.26-1.55 (2H, 5-**H**e, 5-**H**a), 2.26-2.44 [3H, $CHOHC\mathbf{H}_2N$ (2H), 2-**H**a (0.5H), 6-**H**a (0.5H)], 2.56-2.73 [1.5H, 6-**H**e (0.5H), 2-**H**a (0.5H), 2-**H**e (0.5H).

piperidyl]-*N*-phenylpropanamide (β-hydroxyfentanyl) hydrochloride [12]. The carbons were readily distinguished from each other by their multiplicities. The resonance of the carbon bearing the hydroxyl group correlated with a proton multiplet at δ 4.64, which multiplet was assigned to the methine proton bonded to that carbon based on the proton nmr data reported for (±)-*N*-[1-[2-hydroxy-2-(4-fluorophenyl)ethyl]-4-piperidyl]-*N*-phenylpropanamide [13]. The heteronuclear correlation experiment showed that the protons on the other phenylethyl carbon were part of a three proton multiplet in the δ 2.26-2.44 region of the proton spectrum. This represented a slight upfield shift from the position of these resonances in the spectrum of *cis*-3-methylfentanyl.

Of the piperidine ring protons, the 4-Ha resonance was easily identified by its downfield location and its appearance as a doublet of triplets [3b,9-11]. The correlation of this resonance with the carbon resonance at δ 56.90 confirmed the assignment of the latter to the piperidine C-4 carbon. Of the remaining carbon resonances, those due to C-3 were readily differentiated as doublets in the off-resonance spectrum. The correlation of these resonances with the proton multiplet at δ 3.78 identified the latter as the 3-He signal. Since the C-5 signals were expected to be upfield from those of C-2 and C-6 [12], the remaining upfield carbon resonances were assigned to C-5. The correlation of these resonances with the overlapping multiplets assigned to 5-He and 5-Ha provided a confirmation of this assignment. These proton resonances were essentially unchanged from the spectrum of *cis*-3-methylfentanyl [9].

In the carbon-13 nmr spectrum of (±)-*N*-[1-(2-hydroxy-2-phenylethyl)-4-piperidyl]-*N*-phenylpropanamide (β-hydroxyfentanyl) hydrochloride the piperidine 2,6-carbons had appeared as separate resonances due to the molecular asymmetry introduced by the hydroxyl group [12]. Therefore, due to the additional element of asymmetry provided by the *cis*-3-methyl group, the appearance of pairs of resonances (δ 51.50, 55.14 and δ 57.38, 61.20) for the piperidine 2,6-carbons was not surprising. The assignment of these resonances was based on the correlation of the δ 51.50 carbon resonance to a triplet of doublets at δ 2.03 in the proton spectrum. This particular resonance, which in-

Table III

Partial Carbon-13 and Proton NMR Correlations for Compound **4** [a,b]

Carbon-13		Proton				
Signal	Assignment	Signal				Assignment
9.30 (q)	$CH_2\mathbf{C}H_3$	0.97	t		3H	$CH_2C\mathbf{H_3}$
28.56 (t)	$\mathbf{C}H_2CH_3$	1.90	dq		2H	$C\mathbf{H_2}CH_3$
13.41 (q)	3-$\mathbf{C}H_3$	1.17	d	J = 7.0 Hz	3H	3-$C\mathbf{H_3}$
58.04 (t)	**C**-2	2.60-2.75	overlapping m		4H	2-**He**, 2-**Ha**
31.56 (d)	**C**-3	2.60-2.75	overlapping m		4H	3-**He**
56.99 (d)	**C**-4	4.26	dt		1H	4-**Ha**
26.03 (t)	**C**-5	1.22-1.45	overlapping m		2H	5-**He**, 5-**Ha**
46.40 (t)	**C**-6	1.75 2.60-2.75	td overlapping m		1H 4H	6-**Ha** 6-**He**
60.38 (t)	$\mathbf{C}H_2OH$	3.59	m		2H	$C\mathbf{H_2}OH$
69.28 (d)	$C_6H_5\mathbf{C}HN$	3.89	m		1H	$C_6H_5C\mathbf{H}N$

[a] See notes to Table II.
[b] This table includes the following overlapping multiplets observed in the proton nmr spectrum: δ 1.22-1.45 (2H, 5-**He**, 5-**Ha**), 2.60 - 2.75 (4H, 2-**He**, 2-**Ha**, 3-**He**, 6-**He**).

tegrated for half a proton, had been assigned to 6-Ha based on comparisons to proton spectra of fentanyl and *cis*-3-methylfentanyl [9]. Therefore, based on the correlations, the δ 51.50 resonance was assigned to C-6 and the downfield proton doublet at δ 3.02 was assigned to the corresponding 6-He. The assignment of the δ 51.50 resonance meant that the δ 55.14 signal was likewise due to C-6 and that the remaining pair of resonances belonged to C-2. The correlation of the δ 57.38 resonance with the downfield proton doublet at δ 2.93 allowed the assignment of that resonance to a 2-He proton. The remaining protons bonded to the piperidine 2,6-carbons had signals which were part of multiplets. The assignments presented in Table II were based on correlations to the carbon signals.

We noted earlier that the complexity of the nmr spectra on our samples of (±)-*cis*-*N*-[1-(2-hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**3**) was due to the presence of two diastereoisomeric pairs of isomers. In the proton nmr spectrum we observed two doublets at δ 2.93 and 3.02, each of which integrated for half a proton. Since we had assigned these doublets to a 2-He and a 6-He proton, respectively, we wondered if these protons were on different diastereoisomers with their downfield positions being dependent on the hydroxyl group stereochemistry. Following our preparation of compound **3** from ketone **6** [6,7], we attempted to separate the diastereoisomeric components by fractional crystallization. Although our attempts were not entirely successful, we did isolate some fractions enriched in a less soluble component. Proton nmr analysis of these fractions revealed that the patterns at δ 2.03 and 3.02 were enhanced while the doublet at δ 2.93 was diminished. Although this finding did not confirm the assignments, it did indicate that the doublets at δ 2.93 and 3.02 belonged to different diastereoisomers.

Based on the synthetic method, compound **4** was also a mixture of diastereoisomeric components. Nevertheless, the nmr data obtained on the compound (*cf.* Table III) did not show the same doubling of resonances that was observed for compound **3**. A comparison of the data in Tables II and III revealed that the assignments for the propanamide ethyl group, the *cis*-3-methyl group, and the piperidine ring excepting C-6 were very similar between compounds **3** and **4**, as expected on the basis of the structural similarity between these portions of the two molecules. The major difference occurred in the proton nmr spectrum in which the resonances of four piperidine ring protons appeared as a δ 2.60-2.75 multiplet. The assignment of the δ 46.40 carbon resonance as piperidine C-6 followed from its correlation with the 6-Ha triplet of doublets at δ 1.75. The resonance of the carbon bonded to the piperidine ring nitrogen is shifted downfield slightly since it is now also bonded to the aromatic ring. It was distinguished by its multiplicity in the off-resonance spectrum and it correlated with a one proton multiplet at δ 3.89. The hydroxymethyl carbon signal (off-resonance triplet) was located at δ 60.38 and was correlated with a two proton multiplet at δ 3.59. These proton resonances represented a downfield and an upfield shift, respectively, compared to the corresponding proton signals in compound **3**. These shifts were consistent with the structural differences between these portions of the two molecules.

The hydroxymethyl substituent of compound **4** occupies a position in space between the phenylethyl aromatic ring and the piperidine ring. In the proton nmr spectrum of compound **4** an upfield shift of two additional phenyl proton signals is seen, which shift is consistent with some crowding of the phenylethyl aromatic ring by the presence of the hydroxymethyl substituent. In addition, the spectral data implies that the hydroxymethyl substituent occupies a position closer to the piperidine 6-carbon than it is to the 2-carbon, which could explain the upfield shifts observed for the C-6 and 6-Ha resonances compared to their chemical shifts in the spectra on compound **3**. The orientation of the hydroxymethyl substituent toward the C-6 side of the piperidine ring is logical since an orientation toward the C-2 side could be sterically hindered by the 3-methyl substituent. There is no spectral evidence for steric effects involving the 3-methyl substituent.

Biological studies on compounds **4** and **6** are in progress as well as further studies on compound **3**. The biological findings will be the subject of a later report.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary apparatus and are uncorrected. Proton and carbon-13 nmr spectra were recorded in deuteriochloroform on a Bruker WM 250 MHz spectrometer. Chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane. Carbon-13 multiplicities were determined by a single-frequency off-resonance decoupling (sford) experiments. The two-dimensional heteronuclear correlation experiments were run on 103 mg samples. Infrared (ir) spectra were run in methylene chloride on a Shimadzu IR-460 spectrophotometer. Electron-impact mass spectra (ei-ms) were obtained on an AEI MS 902 mass spectrometer. Thin layer chromatographic (tlc) analyses were done on analytical silica gel plates (E. Merck). Unless noted otherwise, anhydrous sodium sulfate was used to dry organic solutions. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN and by Atlantic Microlabs, Inc., Atlanta, GA.

(±)-*cis*-*N*-(3-Methyl-4-piperidyl)-*N*-phenylpropanamide (**2**).

The title compound was prepared using literature procedures [3] and purified by crystallization of the hydrochloride salt from methanol/diethyl ether. A suspension of the hydrochloride salt (20.00 g, 0.071 mole) in water (200 ml) was treated with concentrated ammonium hydroxide until *p*H 10, then extracted with methylene chloride (4 x 200 ml). The combined extracts were dried and evaporated to obtain 18.13 g (104%) of the free base as a pale yellow oil; ir: 3035, 2935, 2805, 2725, 1637, 1592 cm^{-1}; ^{1}H nmr: δ 1.00 (t, 3H, CH_2CH_3), 1.06 (d, 3H, $CHCH_3$), 1.24-1.39 (two overlapping m, 2H, 5Ha and 5He), 1.72 (s, 1H, NH), 1.93 (q, 2H, CH_2CH_3), 2.58-2.72 (two overlapping m, 2H, 3He and 6Ha), 2.81 (dd, 1H, 2Ha), 2.91-3.01 (two overlapping m, 2H, 2He and 6He), 4.53 (m, 1H, 4Ha), 7.06 (broad s, 1H, phenyl proton), 7.37 (m, 4H, phenyl protons). The chemical shift values were in good agreement with data reported in the literature [3b].

(±)-*cis*-*N*-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**3**) and (±)-*cis*-*N*-[1-(2-Hydroxy-1-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**4**) (Styrene Oxide Approach).

A.

A mixture of compound **2** (10.35 g, 0.042 mole) and styrene oxide (5.58 g, 0.046 mole) was heated 9 hours at 100° (oil bath temperature). After cooling, the sticky residue was dissolved in methanol and treated with a solution of hydrogen chloride gas in methanol. Evaporation of the resultant solution to dryness yielded a crude hydrochloride salt (16.24 g), which was a mixture by tlc analysis. Efforts to effect purification by recrystallization of the mixture were unsuccessful. Consequently, the crude salt was converted to the free base (dissolve in water, neutralize with sodium bicarbonate, extract with methylene chloride) and the recovered base (14.02 g) was chromatographed on silica gel using a methylene chloride to 1.5% methanol/methylene chloride gradient. Partially purified fractions were combined and rechromatographed using a methylene chloride to 1% methanol/methylene chloride gradient. From the chromatographies was isolated a free base fraction identical by tlc to the major component of the reaction mixture. This base was dissolved in diethyl ether and the solution was bubbled with hydrogen chloride gas to generate the hydrochloride salt. Recrystallization from methanol/diethyl ether afforded 4.49 g (26%) of compound **3** hydrochloride as a white solid, mp 178-180°; tlc: single spot, R_f 0.49 [chloroform:methanol:concentrated ammonium hydroxide (96:4:4 drops/100 ml)]; ei-ms: m/z 259 (100), 216 (21), 203 (46), 160 (46). Using the procedure described above a 120 mg sample of the salt was converted to the free base (103 mg) for nmr analysis; ^{1}H nmr: δ 3.90 (broad s, 1H, OH), 7.04 (broad s, 1H, phenyl proton), 7.18-7.34 (m, 9H, phenyl protons); ^{13}C nmr: δ 125.39, 126.95, 127.68, 127.85, 128.67, 129.99, 130.29 (d, phenyl carbons), 140.21, 141.89 (s, phenyl carbons), 173.91 (s, $NCOCH_2CH_3$). The remaining proton and carbon-13 resonances are summarized in Table II.

Anal. Calcd. for $C_{23}H_{31}ClN_2O_2 \cdot 0.25H_2O$: C, 67.80; H, 7.79; Cl, 8.70; N, 6.87. Found: C, 67.82; H, 7.82; Cl, 8.66; N, 6.87.

Also isolated from the chromatographies was a minor free base fraction which was dissolved in diethyl ether and treated with hydrogen chloride gas. Recrystallization of the resultant salt from methanol/diethyl ether yielded 0.75 g (4%) of compound **4** hydrochloride as a white solid, mp 218-220°; tlc: single spot, R_f 0.34 [chloroform:methanol:concentrated ammonium hydroxide (96:4:4 drops/100 ml)]; ei-ms: m/z 334 (100), 216 (13), 186 (11), 160 (21), 118 (32). A 118 mg sample of the salt was converted to the free base (103 mg) for nmr analysis; ^{1}H nmr: δ 3.46 (broad s, 1H, OH), 6.99 (broad s, 1H, phenyl proton), 7.12 (m, 2H, phenyl protons), 7.30 (m, 7H, phenyl protons); ^{13}C nmr: δ 127.42, 127.62, 127.77, 128.30, 128.62, 130.00, 130.21 (d, phenyl carbons), 135.65, 140.30 (s, phenyl carbons), 173.85 (s, $NCOCH_2CH_3$). The remaining proton and carbon-13 resonances are summarized in Table III.

Anal. Calcd. for $C_{23}H_{31}ClN_2O_2 \cdot 0.25H_2O$: C, 67.80; H, 7.79; Cl, 8.70: N, 6.87. Found: C, 67.88; H, 7.81; Cl, 8.69; N, 6.89.

B.

A mixture of compound **2** (2.80 g, 0.0114 mole) and Woelm 200 super I neutral alumina (100 g) in diethyl ether (700 ml) was stirred 10 minutes. A solution of styrene oxide (6.80 g, 0.0565 mole) in diethyl ether (50 ml) was then added dropwise over a 15 minute period. Following the addition, the resultant mixture was stirred 2 hours at room temperature. Methanol (200 ml) was then added, the mixture filtered through a Celite pad, and the filtrate evaporated. The crude product was partitioned between toluene (400 ml) and saturated sodium bicarbonate solution (400 ml). The layers were separated, and the toluene layer was extracted with 10% citric acid (4 x 150 ml). The combined acidic extracts were adjusted to *p*H 10 with concentrated ammonium hydroxide and extracted with chloroform (4 x 150 ml). The combined organic extracts were dried and evaporated to obtain an amber oil (4.30 g) which by tlc was largely a mixture of compounds **3** and **4**. Subsequent flash chromatography on silica gel using ethyl acetate:hexanes (1:1) provided compound **3** (1.45 g, 35%) and compound **4** (2.14 g, 51%), both as colorless oils. By tlc and nmr these free bases were identical to those obtained from the initial preparation.

Compound **3** was treated with dioxane (2 ml) which had been saturated with hydrogen chloride gas, and the resultant salt was recrystallized from ethyl acetate/methanol to give the hydrochloride salt (1.30 g) as a white solid, mp 183-185°; tlc: single spot, R_f 0.60 [ethyl acetate:hexanes:concentrated ammonium hydroxide (50:50:5 drops/100 ml)].

Anal. Calcd. for $C_{23}H_{31}ClN_2O_2 \cdot 0.25H_2O$: C, 67.80; H, 7.79; Cl, 8.70; N, 6.87. Found: C, 67.75; H, 7.79; Cl, 8.74; N, 6.88.

Compound **4** was treated with dioxane (2 ml) which had been saturated with hydrogen chloride gas, and the resultant salt was recrystallized from ethyl acetate/methanol to give the hydrochloride salt (0.82 g) as a white solid, mp 215-217°; tlc: single spot, R_f 0.45 [ethyl acetate:hexanes:concentrated ammonium hydroxide (50:50:5 drops/100 ml)].

Anal. Calcd. for $C_{23}H_{31}ClN_2O_2$: C, 68.55; H, 7.75; Cl, 8.80; N, 6.95. Found: C, 68.63; H, 7.84; Cl, 8.83; N, 6.92.

(±)-*cis*-*N*-[1-(2-Oxo-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**6**).

A suspension of compound **2** (5.00 g, 0.020 mole), 2-bromoacetophenone (2.02 g, 0.010 mole) and potassium iodide (0.24 g, 0.001 mole) in toluene (50 ml) was stirred at 45° for 2 hours, after which time tlc analysis indicated the absence of 2-bromoacetophenone. The reaction mixture was diluted with water (75 ml) and the resultant layers were separated. The aqueous layer was extracted with toluene (3 x 150 ml). The combined toluene extracts were washed with water (200 ml), then combined with the original toluene layer. The combined organics were dried and evaporated to obtain a yellow oil (3.75 g). A solution of the oil in diethyl ether (200 ml) was bubbled with hydrogen chloride gas, precipitating a sticky yellow solid. The ether was evaporated and the residual material was dissolved in methanol. After treatment with Norit, the solution was evaporated to give a pale yellow solid. Two recrystallizations from ethyl acetate/methanol followed by vacuum drying 24 hours at 60° afforded 2.36 g (58%) of compound **6** hydrochloride as colorless crystalline flakes, mp 225.5-227° (lit 225-226° [7]); tlc: single spot, R_f 0.72 [chloroform:acetone (95:5)].

Anal. Calcd. for $C_{23}H_{29}ClN_2O_2$: C, 68.90; H, 7.29; Cl, 8.84; N, 6.99. Found: C, 68.99; H, 7.28; Cl, 8.85; N, 6.81.

A solution of the hydrochloride salt (2.15 g, 0.00536 mole) in water (100 ml) was adjusted to *p*H 10 with concentrated ammonium hydroxide, then extracted with chloroform (3 x 150 ml). The combined extracts were dried and evaporated to give 1.58 g (81%) of the title compound as a yellow oil, tlc: single spot, R_f 0.72 , [chloroform:acetone (95:5)]; ir 3045, 2955, 2930, 2790, 1678, 1649, 1592 cm^{-1}; ^{1}H nmr: δ 1.00 (t, 3H, CH_2CH_3), 1.10 (d, 3H, $CHCH_3$), 1.28 (m, 1H, 5He), 1.47 (octet, 1H, 5Ha), 1.93 (q, 2H, CH_2CH_3), 2.19 (dt, 1H, 6Ha), 2.44 (dd, 1H, 2Ha), 2.74-2.84 (overlapping m, 3H, 2He, 3He and 6He), 3.63 (s, 2H, $COCH_2N$), 4.43 (dt, 1H, 4Ha), 7.05 (broad s, 1H, phenyl proton), 7.35-7.51 (m, 7H, phenyl protons), 7.99 (d, 2H, phenyl protons); ^{13}C nmr: δ 9.24 (CH_2CH_3), 13.12 ($CHCH_3$), 25.82 (C-5), 28.56 (CH_2CH_3), 31.06 (C-3), 53.61 (C-6), 56.76 (C-4), 59.64 (C-2), 64.75 ($COCH_2N$), 127.57, 127.89, 128.04, 128.55, 128.68, 129.94, 130.26, 132.63 (d, phenyl carbons), 135.63, 140.16 (s, phenyl carbons), 173.92 (s, $NCOCH_2CH_3$), 196.82 (s, $COCH_2N$).

(±)-*cis*-*N*-[1-(2-Hydroxy-2-phenylethyl)-3-methyl-4-piperidyl]-*N*-phenylpropanamide (**3**) (Ketone Reduction Approach).

To a stirred solution of compound **6** (2.50 g, 0.007 mole) in methanol (125 ml) was added solid sodium borohydride (1.70 g, 0.045 mole) portionwise. The resultant reaction mixture was refluxed 4 hours, after which time tlc analysis indicated complete reaction. The reaction mixture was evaporated and the yellow residue was suspended in water (125 ml). The aqueous suspension was then extracted with chloroform (3 x 125 ml). The combined extracts were dried and evaporated to obtain a yellow oil (2.38 g). This was combined with a similar product from an identical reaction and the combined sample was chromatographed on alumina (96 g), eluting with chloroform. The chromatography afforded 3.47 g (68%) of the title compound as a yellow oil. Analysis by tlc and nmr showed this material to be identical to the compound **3** prepared utilizing the styrene oxide approach, although the ratios of diastereoisomeric pairs present in the product samples appeared to differ slightly from sample to sample. A solution of the oil in diethyl ether was bubbled with hydrogen chloride gas to generate the hydrochloride salt. Recrystallization from methanol/diethyl ether yielded 2.80 g of compound **6** hydrochloride as pale off-white crystals, mp 183-190° (lit 206-207° [7]). The melting point difference was attributed to the difference in isomeric composition (presence of two diastereoisomeric pairs in the synthetic sample *versus* presence of one diastereoisomeric pair in the reported sample [7]).

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