Synthesis of (1′,2′-*trans*)-3-Phenyl-1-[2′-(*N*-pyrrolidinyl)cyclohexyl]-pyrrolid-2-ones as κ-Selective Opiates

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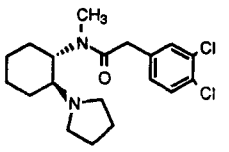
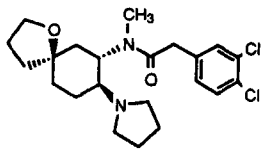
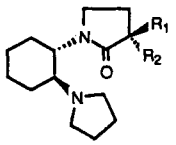
Abstract □ (1′,2′-*trans*)-3-Phenyl-1-[2′-(*N*-pyrrolidinyl)cyclohexyl]pyrrolid-2-ones (**1** and **2**) and their 3,4-dichlorophenyl analogues (**4** and **5**) were synthesized as lactam analogues of U-50,488 (I; a κ-opiate analgesic developed by Upjohn Company). Compounds **1** and **2** were found to be oxidized by air, in the presence of a strong base, to the 3-hydroxylated derivative **3**. Compound **4** gave slightly higher κ-affinity (K_i = 10 nM) than I, with about half the κ-selectivity (μ/κ = 23). Compounds **1** and **3** showed weaker κ-binding (K_i = 400 nM), with about the same κ-selectivity as **4**. Compound **5**, a diastereomer of **4**, gave significantly weaker and less selective κ-binding than **4**; likewise, **2** is a weaker and less selective κ-binder than **1**. The binding data of intermediate compounds having the basic skeleton of I seem to reflect the importance of lipophilicity and the detrimental effects of bulky substituents on the amide nitrogen. It is likely that the binding conformation of I at the opiate receptors approaches that of the lactam analogue **4**.



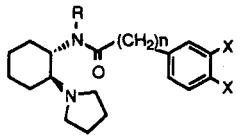
I (U-50, 488)



II (U-62, 066)



1: R_1 = H, R_2 = Ph
2: R_1 = Ph, R_2 = H
3: R_1 = OH, R_2 = Ph
4: R_1 = H, R_2 = 3,4-dichlorophenyl
5: R_1 = 3,4-dichlorophenyl, R_2 = H



	R	n	X
18	H	1	H
19	$(CH_2)_3H$	1	Cl
20	$(CH_2)_3OH$	1	Cl
21	$(CH_2)_3OH$	1	H
22	$(CH_2)_2OH$	1	H
23	$(CH_2)_2OH$	0	H

In the search of centrally acting analgesics devoid of morphine-like side effects, κ-selective opiates have received considerable attention in recent years. Compounds U-50,488 (I) and U-62,066 (II), developed by Upjohn Company, are good examples of κ-opiate analgesics.[1,2] Compound II has been in clinical trial, while other analogues of I have appeared in the literature.[3,4] κ-Agonists such as I are attractive because they have been shown to give good antinociception,[5–7] a milder form of physical dependence distinct from morphine dependence,[8] with limited effects on respiratory and gastrointestinal tracts,[9] despite the fact they produce sedation and diuresis as side effects.[9,10]

The structure and conformation of the arylamide side-chain of I seem to be the key for κ-binding affinity and selectivity. For example, simply shortening the $N(Me)COCH_2Ar$ side-chain to N(Me)COAr inverts receptor binding selectivity from kappa (κ) to mu (μ).[1,11] In order to explore the active conformation of I and to help define the structural requirements for binding to the opiate κ-receptor, we have been synthesizing a series of conformationally constrained analogues of I. In this report, we describe the synthesis and opiate receptor affinities of five-membered lactam analogues of I (**1–5**). Compounds **1–5** are structurally related to I in that the amide linkage in I is replaced by a substituted pyrrolidone ring.

Results and Discussion

Chemistry—The two synthetic approaches developed for these lactam analogues are exemplified by the preparation of **1** and **2** as shown in Schemes I and II. The first one is based on lactam formation via cyclization of a haloamide (Scheme I). The key intermediates are the diamine **8** and the chloroacid **12**. The *trans*-diamine **8** was prepared from the aziridine **7** by ring cleavage with pyrrolidine, with NH_4Cl as the catalyst. The aziridine **7** was prepared from cyclohexene oxide via the azido alcohol **6**.[12] The preparation of the chloroacid **12** starts from phenylacetonitrile. An ethylcarboxyl group was introduced first to ensure monoalkylation in the following step. Compound **9** was then smoothly alkylated with 1-bromo-2-chloroethane to give the chloronitrile **10**. De-ethylcarboxylation was effected with $Na_2CO_{3(aq.)}$:CH_3OH at 0 °C to give **11**. If stronger bases such as NaOH or higher temperatures were used, intramolecular cyclization of **11** would occur to give 1-phenylcyclopropanecarbonitrile (**14**) as the major product. Hydrolysis of **11** was best effected with conc. $HCl_{(aq)}$ at 100 °C in a sealed vessel to give the chloroacid **12**. Coupling of **12** and **8** was effected with carbonyldiimidazole in THF to give the chloroamide **13**. The crucial cyclization step was successfully effected with K-*t*-butoxide in DMF under N_2 to give a diastereomeric mixture of **1** and **2**, which can be easily separated by chromatography. Based on NMR analysis, the pyrrolidine and pyrrolidone rings in both **1** and **2** are *trans* to each other ($J_{1',2'}$ = 12–13 Hz); but the stereochemistry of C-3 relative to C-1′ and C-2′ cannot be unambiguously assigned without X-ray crystal analysis. The tentative assignment of the stereochemistry of **1** and **2** as shown is based on their receptor binding data and comparison of their dreiding models with the X-ray crystal structure of a κ-selective compound like I[13] (see *Opiate Receptor Binding* section below). If the above cyclization reaction was done without thorough deaerating and protection under N_2, the 3-hydroxylated derivative of **1**, namely **3**, was obtained as the major product. Both **1** and **2** were found to be oxidized to give **3** upon treatment with a

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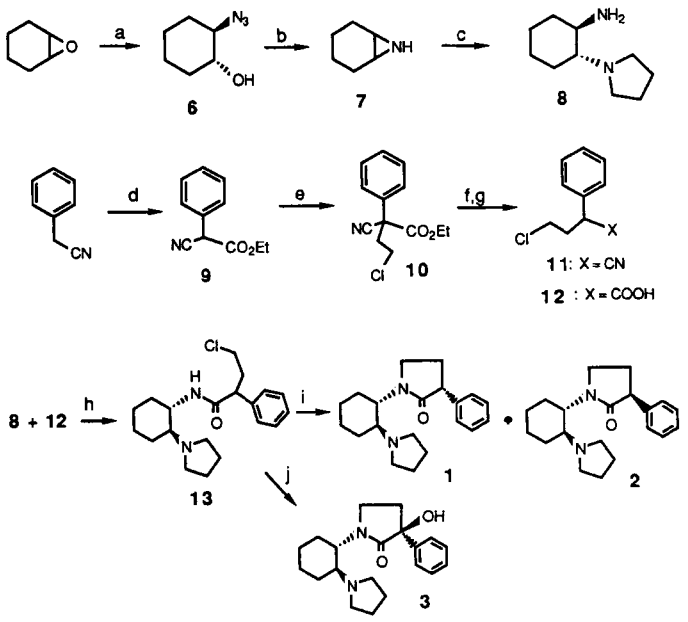
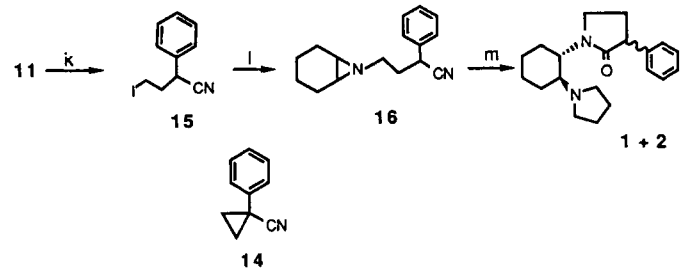


Scheme I—(*a*) NaN_3, acetone, reflux; (*b*) Ph_3P, THF, reflux; (*c*) pyrrolidine, NH_4Cl; (*d*) $CO(OEt)_2$, $NaNH_2$, ether; (*e*) BrC_2H_4Cl, K-*t*-butoxide, DMF; (*f*) Na_2CO_3, aq. CH_3OH; (*g*) conc. HCl, sealed vessel, 100 °C; (*h*) carbonyldiimidazole, THF; (*i*) K-*t*-butoxide, DMF, N_2; (*j*) K-*t*-butoxide, DMF, O_2.



Scheme II—(*k*) NaI, acetone, reflux; (*l*) **7**, $NaHCO_3$, CH_2Cl_2; (*m*) pyrrolidine, dioxane:H_2O.

strong base in DMF in the presence of air. It is known that enolate anions can react with molecular oxygen to give α-hydroperoxides, which can then be reduced to the corresponding α-hydroxycarbonyl compounds. In our case, however, the intermediate peroxide seems to be stereoselectively converted to the tertiary alcohol **3** in the absence of any added reducing agent by mechanisms yet to be elucidated.

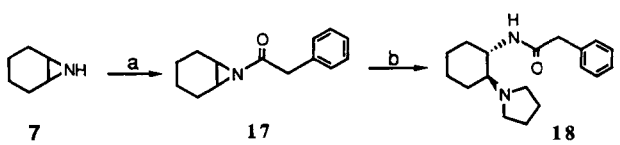
The second approach for the synthesis of **1** and **2** makes use of the chemistry of acid-catalyzed ring cleavage of *N*-alkylaziridines (Scheme II). Compound **16**, the key intermediate, was obtained by reacting the aziridine **7** with the iodide **15** derived from the chloronitrile **11**. The *N*-alkylation was a slow reaction under the condition used ($NaHCO_3$:CH_2Cl_2). After refluxing for 1 day, **16** was obtained in a yield of 30%, with 43% of the starting iodide **15** recovered unchanged. Although the use of stronger bases, more polar solvents, or higher temperatures accelerated the reaction, increased amounts of the undesired **14** from intramolecular cyclization of **15** were also obtained. By reacting **16** with pyrrolidine in the presence of NH_4Cl, the desired lactams (**1** and **2**) were obtained in good yields. Therefore, in a one-pot operation, we have effected aziridine ring opening, nitrile hydrolysis, and lactam formation. The 3,4-dichlorophenyl analogues of **1** and **2**, namely **4** and **5**, were also prepared according to Scheme I, substituting 3,4-dichlorophenylacetonitrile for phenylacetonitrile as the starting material.

Compounds **18**–**23** were obtained as intermediates during our exploration of alternative synthesis of **1** and **2**. Compound **18** was obtained via ring cleavage of the acylaziridine **17** with pyrrolidine (Scheme III). Compound **19**, the *N*-propyl analogue of **I**, was prepared in a manner similar to that for **I**.[2] The preparation of **22**, the *N*-hydroxyethyl analogue of **I**, is shown in Scheme IV; **20**, **21**, and **23** were prepared similarly. Since these compounds all have the basic skeleton of **I**, they were also subjected to the opiate receptor binding assay.

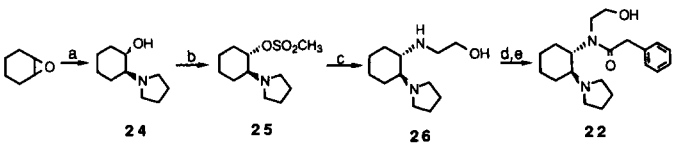
Opiate Receptor Binding—Table I gives the receptor affinities of compounds synthesized in this study. The data of **I** and morphine are included for comparison. Numbers in the last column (μ/κ) are indicators of κ-selectivity.

As with **I**, none of the compounds tested showed any significant δ-affinity. Among the five lactam analogues, **4** gave slightly higher κ-affinity (K_i = 10 nM) than **I**, with about half the κ-selectivity (μ/κ = 23). Compound **5**, being diastereomeric to **4** with respect to the stereochemistry of C-3, showed significantly reduced κ-affinity and κ-selectivity compared with **4**. Examination of the dreiding models of **4** and **5** in their assigned stereochemistry reveals that if we overlap the pyrrolidine ring and the amide linkage in these two molecules with those of the crystal structure of a κ-selective analogue of **I**, namely (*S,S-trans*)-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[b]thiophene-4-acetamide monohydrochloride,[13] the 3,4-dichlorophenyl ring in **4** is in the same region as the lipophilic thiophene ring in the crystal structure; however, the 3,4-dichlorophenyl ring in **5** is not. Compound **1**, the deschloro analogue of **4**, showed much weaker κ-affinity (K_i = 416 nM) and about the same κ-selectivity as **4**. Compound **2**, the deschloro analogue of **5** and a diastereomer of **1**, gave even weaker and less selective κ-binding. It is not immediately apparent whether the observed potency difference between **1** and **4** is due to the lipophilic effect ($+\pi$) or the electron-withdrawing effect ($+\sigma$) of the dichloro substitution. However, in a recent study of a series of compounds like **I**, namely *N*-[(2-aminocyclohexyl)aryloxy]acetamides, as κ-agonists,[13] it was shown that the analogue with the electron-withdrawing 4-nitro-3-trifluoromethyl substitution is much less active than the 3,4-dichloro analogue. It was thus suggested that "the $+\pi$, rather than the $+\sigma$ effect of the chlorine substituents is primarily responsible for increased potency". Compound **3**, the 3-hydroxy derivative of **1**, showed a binding profile very similar to that of **1**, in terms of both potency and κ-selectivity. It is based on this similarity that we tentatively assign the stereochemistry of **3** as shown, with its phenyl ring in the same orientation as that of **1**.

Compound **13**, the direct synthetic precursor of **1** and **2**, showed only weak κ-binding. It is rather surprising to see the large reduction in both binding affinity and κ-selectivity, which resulted from the replacement of the *N*-methyl group in **I** by a bulkier *n*-propyl group, as demonstrated by **19**. The nor-compound **18** showed even weaker κ-affinity. None of the



Scheme III—(*a*) $PhCH_2COCl$, Et_3N, ether; (*b*) pyrrolidine, reflux.



Scheme IV—(*a*) Pyrrolidine, H_2O, sealed vessel, 80 °C; (*b*) CH_3SO_2Cl, Et_3N, CH_2Cl_2, 0 °C; (*c*) 2-aminoethanol, THF, reflux; (*d*) $PhCH_2COCl$, Et_3N, CH_2Cl_2; (*e*) $KOH_{(aq)}$:CH_3OH.

four *N*-hydroxyalkyl analogues (**20**–**23**) showed any measurable binding towards the κ receptor, while two of them (**20** and **22**) gave marginal μ-affinity. Whether the loss of opiate affinity is due to the hydrophilic nature of the hydroxyalkyl groups or unfavorable steric effects remains to be elucidated.

Conclusions

Five-membered lactam analogues of **I** (**1**–**5**) have been synthesized in this study. The opiate receptor affinities of these compounds depend largely on the orientation of the phenyl ring as determined by the stereochemistry of C-3, and whether the 3,4-dichloro substitution is present.

Compound **4**, the more active of the two diastereomeric dichloro analogues, showed a receptor binding profile which is qualitatively similar to that of **I**. Based on the above observation and a study of the dreiding models of the parent compound and analogues, it may be concluded that the binding conformation of **I** at the receptor is similar to that of **4**. The increased potencies of **4** and **5** relative to the unsubstituted analogues (**1** and **2**) may be mainly due to the lipophilic ($+\pi$) effect of the dichloro substitution. Synthetic methods developed in this study could be applied to the preparation of six- and seven-membered lactam analogues of **I**, and the SAR data accumulated could lead to a better understanding of the structural requirements for binding to the κ-opiate receptor, and may lead to the discovery of better analgesics.

Experimental Section

Synthesis—Melting points were taken in a capillary tube using a Büchi SMP-20 melting point apparatus. The IR spectra were determined with a Perkin-Elmer model 577 or 983 spectrometer. The NMR spectra were recorded on a Bruker AM-300 or AM-80 spectrometer; chemical shifts were recorded in parts per million downfield from Me_4Si. Mass spectra were recorded on a Finnigan TSQ-46C spectrometer; high-resolution mass spectroscopy (HRMS) was performed with a JEOL JMS-HX 110 spectrometer. Elemental analyses were done with a Perkin-Elmer 240C instrument. The TLC was done with Merck (Art. 5717) silica gel plates and visualized with UV (254 nm) light or upon heating with 2% phosphomolybdic acid in ethanol. Flash column chromatography was done on Merck 40–63-μm silica gel. Reagent grade THF was distilled from sodium benzophenone prior to use. Other anhydrous solvents were distilled from CaH_2 and stored over 4-Å molecular sieves until the time of use.

The C—H and H—H 2D correlation NMR spectra of **1**–**3** and **13**, and the assignments of ^1H and ^{13}C chemical shifts are available from the author.

7-Azabicyclo[4,1,0]heptane (7)—A mixture of cyclohexene oxide (15 g, 0.15 mol) and sodium azide (25 g, 0.38 mol) in acetone:H_2O (1:1) was refluxed for 14 h. After evaporation of the solvents, the residue was distilled (Kugel-rohr) under reduced pressure to give 21.5 g (99%) of 2-azidocyclohexanol (**6**): bp 70–71 °C (1.5 mmHg); IR (neat): 3600–3100 (br), 2080 (s, N_3) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 3.18 (2H, m), 2.28 (1H, s), 1.94 (2H, m), 1.72 (2H, m), and 1.22 (4H, m); MS: *m/z* 141 (M^+), 81, 57, 43 (base peak).

Compound **6** (15.6 g, 0.11 mol) and triphenylphosphine (29 g, 0.11 mol) were dissolved in THF (150 mL). After being refluxed for 4 h, the solvent was evaporated. Kugel-rohr distillation under reduced pressure gave **7** (10.7 g, 96%): mp 20–21 °C; bp 149–50 °C; IR (neat): 3500–3100 (br, NH), 2960–2850 (s, CH), 1430 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ: 2.06 (2H, m), 1.70 (4H, m), and 1.15 (5H, m); MS: *m/z* 97 (M^+), 96, 81, 69, 41 (base peak).

***trans*-2-(*N*-Pyrrolidinyl)-cyclohexylamine (8)**—A mixture of **7** (5.47 g, 56.4 mmol), NH_4Cl (0.30 g, 5.61 mol), pyrrolidine (8 g, 112.7 mmol), and H_2O (50 mL) was heated under reflux at 110 °C for 16 h. The mixture was cooled to room temperature and extracted with CH_2Cl_2. The combined extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was distilled (Kugel-rohr) under reduced pressure to give **8** (4.66 g, 50%): IR (neat): 3600–3100 (NH_2) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$) δ: 2.56 (2H, m), 2.46 (3H, m), 2.21 (1H, dd), 1.88 (1H, m), 1.56–1.70 (9H, m), and 1.24–0.99 (4H, m); MS: *m/z* 168 (M^+), 110 (base peak), 97, 84, 70.

Ethyl 4-Chloro-2-cyano-2-phenylbutyrate (10)—In a flame-dried flask under N_2 was placed K-*t*-butoxide (10.1 g, 89.6 mmol) and dry DMF (50 mL). While the mixture was stirred under N_2 at room temperature, ethyl phenylcyanoacetate (**9**; 11.3g, 59.7 mmol), prepared according to the literature,[14] was added in a dropwise manner. After being stirred for an additional 0.5 h, 1-bromo-2-chloroethane (12.8 g, 89.6 mmol) was added in a dropwise manner via a syringe. The stirring was continued for 24 h. The reaction mixture was then quenched with $NH_4Cl_{(aq)}$ and extracted with ether. The combined extracts were concentrated, and the residual DMF was removed by Kugel-rohr distillation. The residue was flash chromatographed (silica, 5% ether in pet. ether) to give **10** (15 g, 98%): IR (KBr): 2260 (CN), 1750 (s, CO), 1250, 1205 cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 7.57–7.38 (m, 5H), 4.25 (q, J = 7.2 Hz, 2 H), 3.70–3.45 (m, 2H), 2.90–2.57 (m, 2H), and 1.25 (t, J = 7.2 Hz, 3H); MS: *m/z* 251 (M^+), 179, 143, 130 (base peak), 116, 63.

4-Chloro-2-phenylbutyronitrile (11)—A solution of **10** (15 g, 59 mmol) in methanol (100 mL) was stirred at 0 °C while saturated $K_2CO_{3(aq)}$ (20 mL) was added. After being stirred for 3 h at 0 °C, the mixture was neutralized with conc. $HCl_{(aq)}$ and evaporated to remove methanol. The resulting mixture was extracted with ether. The combined ether extracts were washed with H_2O and brine, dried ($MgSO_4$), and concentrated to give crude **11** (10.4 g, 98%), which was used in the following step without further purification. Flash chromatography gave an analytical sample: IR (neat): 3000, 2220 (CN), 1600, 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 (5H, m), 4.12 (1H, t, J = 7.6 Hz), 3.68 (1H, m), 3.53 (1H, m), 2.40 (1H, m), and 2.26 (1H, m); MS: *m/z* 179 (M^+), 143, 130 (base peak), 116, 63.

4-Chloro-2-phenylbutyric acid (12)—A mixture of **11** (2.0 g, 11 mmol) and conc. $HCl_{(aq)}$ (15 mL) was sealed in a 50-mL flask and heated to 100 °C for 12 h. The mixture was cooled, diluted with H_2O, and extracted with ether. The combined extracts were washed, dried ($MgSO_4$), and evaporated to give **12** (1.15 g, 52%): mp 61–64 °C; IR (neat): 3500–2400 (s, COOH), 1700 (s, CO) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 8.86 (1H, s), 7.19 (5H, s), 3.77 (1H, dd, J = 8.2, 8.9 Hz), 3.36 (2H, m), and 2.21 (2H, m); MS: *m/z* 198 (M^+), 163, 118 (base peak), 91.

4-Chloro-2-phenyl-*N*-[2′-(*N*-pyrrolidinyl)cyclohexyl]butyramide (13)—A solution of **12** (0.5 g, 2.5 mmol) in anhydrous THF (2 mL) was stirred at 0 °C under N_2 while 1,1′-carbonyldiimidazole (0.37 g, 2.3 mmol) in anhydrous THF (2 mL) was added in a dropwise manner. After being stirred for 1 h, a solution of **8** (0.5 g, 3 mmol) in THF (2 mL) was added in a dropwise manner. The reaction mixture was allowed to warm to room temperature and was stirred for 2 h. Ether (30 mL) and $Na_2CO_{3(aq)}$ (2 mL) were then added to the mixture. The organic layer was separated, washed (brine), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was flash chromatographed (silica, 3–5% CH_3OH in CH_2Cl_2) to give **13** (0.66 g, 66%) as elongated crystals from acetone; mp 94–98 °C; IR (neat): 3260 (NH), 1650 (s, CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.20 (m, 5H), 3.68 (t, J = 7.5 Hz, 1H), 3.58–3.48 (m, 1H), 3.42–3.34 (m, 1H), 2.64–2.52 (m, 2H), 2.44–2.32 (m, 4H), 2.22–2.11 (m, 1H), 1.74–1.60 (m, 2H), 1.50–1.41 (m, 5H), and 1.30–1.02 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 175.0, 141.5, 128.5, 127.9, 126.6, 59.9, 53.0, 48.5, 48.1, 41.4, 30.2, 28.2, 24.9, 24.8, 24.0, and 23.3; MS: *m/z* 349 (M^+), 313, 151 (base peak), 110, 91.

Anal.—Calc. for $C_{20}H_{29}N_2O$: C, 62.34; H, 7.79; N, 7.27. Found: C, 62.38; H, 8.07; N, 7.19.

The mp of the HCl salt of **13** was 181–183 °C (isopropanol:EtOAc).

4-Iodo-2-phenylbutyronitrile (15)—A solution of **11** (0.5 g, 2.79 mmol) and NaI (0.8 g, 4.56 mmol) in acetone (5 mL) was refluxed for 24 h. The precipitate was filtered off and the filtrate was concentrated under reduced pressure. The residue was picked up in ether and H_2O.

Table I—Opiate Receptor Binding Affinities (K_i, nM)

Compound	Mu (μ)	Kappa (κ)	Delta (δ)	μ/κ
Morphine	38	1870	>10 000	0.02
I (U-50,488)	825	15	>10 000	55
1	>10 000	416 (±34)	>10 000	>24
2	8530 (±160)	672 (±327)	>10 000	13
3	>10 000	382 (±56)	>10 000	>26
4	225	10	3420	23
5	864	92	8200	9.4
18	7680 (±410)	3600 (±200)	>10 000	2.1
19[a]	2620 (±1100)	1430 (±270)	>10 000	1.8
20[a]	6240 (±2340)	>10 000	>10 000	<0.6
21[a]	>10 000	>10 000	>10 000	—
22	7650 (±2800)	>10 000	>10 000	<0.76
23[a]	>10 000	>10 000	>10 000	—
13	>10 000	3850 (±750)	>10 000	>2.6

[a] See ref 16 for analytical data and text for structures.

The ether layer was separated, washed with brine, dried ($MgSO_4$), and evaporated to give **15** (0.73 g, 88%): IR (neat): 3000, 2920, 2850, 2220 (CN), 1600, 1500, 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.34 (5H, m), 4.01 (1H, t, J = 7.4 Hz), 3.27 (1H, m), 3.12 (1H, m), 2.42 (1H, m), 2.27 (1H, m); MS: m/z 271 (M^+), 155, 116 (base peak).

7-[(3'-Cyano-3'-phenyl)propyl]-7-azabicyclo[4,1,0]heptane (16)—A solution of **15** (3.89 g, 14.5 mmol) in dry CH_2Cl_2 (4 mL) was added in a dropwise manner to a stirred mixture of **7** (1.40 g, 14.5 mmol) and $NaHCO_3$ (2.34 g, 28.9 mmol) in dry CH_2Cl_2 (10 mL). The resulting mixture was refluxed for 14 h. The reaction mixture was then cooled and extracted with CH_2Cl_2. The combined extracts were washed with H_2O (10 mL) and brine (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography (silica, 7–10% ether in pet. ether) of the residue gave **16** (1.40 g, 30%) and unreacted **15** (1.67 g, 43%). Compound **16**: IR (neat): 3010, 2212 (CN), 1600, 1480, 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.3 (5H, m), 4.12 (1H, m), 2.40 (2H, m), 2.15 (2H, m), 1.87 (4H, m), 1.51 (1H, m), 1.50 (1H, m), 1.33 (2H, m), and 1.25 (2H, m); ^{13}C NMR (75 MHz, C_6D_6): δ 129.0, 128.0, 127.3, 57.3, 38.6, 37.8, 36.1, 34.9, 24.5, 20.5, and 20.4; MS: m/z 241 (M^+), 111 (base peak), 96.

(1',2'-*trans*)-3-Phenyl-1-[2'-(*N*-pyrrolidinyl)cyclohexyl]-2-pyrrolidinones (1 and 2)—*Method A (cf. Scheme II)*—A solution of **16** (1.02 g, 4.2 mmol), NH_4Cl (0.14 g, 2.6 mmol), and pyrrolidine (0.6 g, 8.5 mmol) in H_2O:1,4-dioxane (1:1) was refluxed for 48 h. The mixture was concentrated under reduced pressure, H_2O was added, and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. The residue was flash chromatographed (silica, 3.5–10% CH_3OH in CH_2Cl_2) to give 0.65 g of **1** and 0.41 g of **2** (total yield = 80.1%).

Compound **1**: R_f = 0.59 (CH_2Cl_2:CH_3OH = 7:1); IR (KBr): 3010, 1665 (s, CO), 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.18 (m, 5H), 4.05 (td, J = 11.3, 3.9 Hz, 1H), 3.63 (q, J = 4.3 Hz, 1H), 3.50 (q, J = 8.3 Hz, 1H), 3.33 (td, J = 9.1, 3.7 Hz, 1H), 2.79–2.68 (m, 2H), 2.53–2.36 (m, 3H), 1.97–1.68 (m, 10H), and 1.53–1.10 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 174.5, 141.5, 128.4, 127.8, 126.6, 58.8, 52.9, 49.2, 46.9, 41.0, 30.3, 28.2, 25.22, 25.15, 23.7, and 22.0; MS: m/z 313 (M^+), 151 (base peak), 110, 97, 69.

Anal.—Calc. for $C_{20}H_{28}N_2O(½\ H_2O)$: C, 67.13; H, 8.39; N, 7.83. Found: C, 67.32; H, 8.71; N, 7.97. The HCl salt of **1** appeared as colorless prisms (acetone:isopropanol = 20:1), with a mp of 180–182 °C.

Compound **2**: R_f = 0.46 (CH_2Cl_2:CH_3OH = 7:1); IR (neat): 3020, 1674 (s, CO), 1600, 1500, 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.10 (m, 5H), 4.06 (td, J = 12.8, 4.3 Hz, 1H), 3.76 (t, J = 9.2 Hz, 1H), 3.51 (q, J = 8.4 Hz, 1H), 3.38 (td, J = 8.8, 3.7 Hz, 1H), 2.88–2.73 (m, 4H), 2.62–2.51 (m, 1H), 2.06–1.54 (m, 10H), and 1.33–1.16 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 175.3, 140.3, 128.5, 127.9, 126.7, 60.0, 53.0, 48.5, 48.1, 41.4, 30.2, 28.2, 24.9, 24.8, 24.0, and 23.3; MS: m/z 313 (M^+), 151 (base peak), 110, 97, 69.

Anal.—Calc. for $C_{20}H_{28}N_2O(½\ H_2O)$: C, 67.13; H, 8.39; N, 7.83. Found: C, 66.83; H, 8.41; N, 7.97.

The HCl salt of **2** appeared as colorless needles (acetone), with a mp of 236–238 °C.

Method B (cf. Scheme I)—In a flame-dried flask was placed K-*t*-butoxide (0.09 g, 0.8 mmol) and dry DMF (1 mL). In another flame-dried flask was dissolved 0.2 g of **13** (0.6 mmol) in dry DMF (1 mL). The two solutions were thoroughly deaerated by repeating the freeze-vacuum-N_2-thaw procedure three times, and kept under an atmosphere of N_2. The solution containing **13** was then added in a dropwise manner to the stirred solution of K-*t*-butoxide via a cannula. After being stirred at room temperature for 20 h, H_2O (5 mL) and brine (5 mL) were added, and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was chromatographed as described above to give 0.08 g of **1** and 0.02 g of **2** (total yield = 56%).

3-Hydroxy-3-phenyl-1-[2'-(*N*-pyrrolidinyl)cyclohexyl]-2-pyrrolidinone (3)—Compound **13** (0.5 g, 1.4 mmol) was subjected to the reaction procedure as described in Method B, except the reaction solutions were not deaerated. After the usual work-up and chromatography, 0.18 g of **3** (40% yield) was obtained. Compound **3** was also obtained by reacting either **1** or **2** (0.03 g) with NaH (50%, 0.2 g) in DMF (3 mL) in the presence of air. Compound **3** was obtained as colorless prisms from EtOAc:*n*-hexane; mp 178–180 °C; IR (KBr): 3300 (OH), 3060, 1674 (s, CO), 1598, 1517, 750, 690 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.56–7.52 (m, 2H), 7.32–7.20 (m, 3H), 4.05 (td, J = 3.8 Hz, 1H), 3.40–3.26 (m, 3H), 2.70 (m, 3H), 2.55 (m, 2H), 2.40–2.22 (m, 2H), 1.92–1.71 (m, 8H), and 1.57–1.15 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 174.8, 143.3, 128.3, 127.5, 124.7, 79.3, 59.0, 53.6, 46.9, 38.6, 36.4, 29.8, 25.1, 25.0, 23.8, and 21.8; MS: m/z 329 (M^+), 313, 151, 110 (base peak).

Anal.—Calc. for $C_{20}H_{28}N_2O_2$: C, 73.29; H, 8.63; N, 8.95. Found: C, 73.14; H, 8.53; N, 8.59.

(1',2'-*trans*)-3-(3,4-Dichlorophenyl)-[2'-(*N*-pyrrolidinyl)cyclohexyl]-2-pyrrolidinones (4 and 5)—Compounds **4** and **5** were prepared according to Scheme I, substituting 3,4-dichlorophenylacetonitrile for phenylacetonitrile as the starting material. From 230 mg of 4-chloro-2-(3,4-dichlorophenyl)-*N*-[2'-(*N*-pyrrolidinyl)cyclohexyl] butyramide was obtained 65 mg of **4** and 28.3 mg of **5** (total yield: 44%). Compound **4**: TLC: R_f = 0.68 (CH_2Cl_2:CH_3OH = 5:1); IR (Nujol): 3010, 1682 cm^{-1} (s, CO); ^1H NMR (300 MHz, $CDCl_3$): δ 7.33–7.14 (m, 3H), 4.0 (td, J_1 = 11.28 Hz, J_2 = 3.8 Hz), 3.58 (q, J = 5.17 Hz), 3.46 (q, J = 8.45 Hz), 3.34 (td, J_1 = 9.04 Hz, J_2 = 4.50 Hz), 2.74–2.64 (m, 3H), 2.53–2.37 (m, 3H), 1.90–1.66 (m, 10H), and 1.50–1.13 (m, 3H); MS: m/z 381 (M^+), 151, 110 (base peak), 97, 69; HRMS: calc. for $C_{20}H_{26}OCl_2N_2$, 380.1422; found, 380.1429. Compound **5**: TLC: R_f = 0.54 (CH_2Cl_2:CH_3OH = 5:1); IR (CH_2Cl_2): 3010, 1685 cm^{-1} (s, CO); ^1H NMR (300 MHz, $CDCl_3$): δ 7.37–7.08 (m, 3H), 3.97 (td, J_1 = 11.33 Hz, J_2 = 3.61 Hz), 3.59 (t, J = 9.18 Hz), 3.37 (m, 2H), 2.75–2.68 (m, 3H), 2.51–2.33 (m, 3H), 2.18–1.39 (m, 10H), and 1.35–1.14 (m, 3H); MS: m/z 381 (M^+), 151, 110 (base peak), 97, 69; HRMS: calc. for $C_{20}H_{26}OCl_2N_2$ (M^+), 380.1422; found, 380.1409.

***N*-Phenylacetyl-7-azabicyclo[4,1,0]heptane (17)**—To a stirred solution of aziridine **7** (3.6 g, 37 mmol) and triethylamine (5.7 mL, 40 mmol) in dry ether (20 mL) at 0 °C was added phenylacetyl chloride (6.0 g, 39 mmol) in a dropwise manner. After being stirred for 3 h, the mixture was filtered, and the filtrate was evaporated under reduced pressure to give a yellowish solid, which was crystallized to give **17** (8.0 g, 95%, based on **7**); IR (neat): 3000–2800, 1670 (s, CO) cm^{-1}; ^1H NMR (80 MHz, $CDCl_3$): δ 7.23 (s, 5H), 3.69 (s, 2H), 2.60 (m, 2H), 1.71 (m, 4H), 1.28 (m, 4H); MS: m/z 215 (M^+), 136, 96, 91 (base peak), 81.

***trans*-*N*-[2-(1-Pyrrolidinyl)cyclohexyl]benzene acetamide (18)**—A mixture of **17** (0.52 g, 2.1 mmol) and pyrrolidine (1 mL) was refluxed

under N_2 for 2 h. After removing the excess pyrrolidine by rotary evaporation, the residue was dissolved in 1 M HCl (10 mL), and washed with ether (10 mL). The aqueous layer was then basified with $Na_2CO_{3(aq)}$ and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give a yellowish solid which was crystallized to give 18; colorless needles (*n*-hexane); mp 114–115 °C; IR (nujol): 3280 (NH), 1638 (s, CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.30–7.18 (m, 5H), 6.36 (s, 1H), 3.51 (s, 2H), 3.40 (m, 1H), 2.50–2.38 (m, 6H), 1.70 (m, 2H), 1.56 (m, 5H), 1.34–0.96 (m, 4H); ^{13}C NMR (75 MHz, C_6D_6): δ 170.5, 136.7, 129.6, 128.7, 126.6, 61.7, 52.1, 47.2, 44.6, 32.3, 25.0, 24.6, 23.9, 22.6; MS: *m/z* 286 (M^+), 195, 151, 110 (base peak), 91, 70.

Anal.—Calc. for $C_{18}H_{26}N_2O$: C, 75.48; H, 9.15; N, 9.78. Found: C, 75.27; H, 9.15; N, 9.73.

***trans*-2-(*N*-Pyrrolidinyl)cyclohexanol (24)**—A mixture of cyclohexene oxide (50 g, 0.51 mol), pyrrolidine (43.5 g, 0.61 mol), and H_2O (42.5 mL), was sealed in a reaction vessel after deaerating, and heated to 70–90 °C for 28 h. The mixture was cooled and extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Distillation of the residue (80 °C, 10 mmHg) gave 24 (69 g, 80%): IR (neat): 3600–3010 (OH), 2960, 2850 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.0 (OH), 3.28 (m, 1H), 2.64 (m, 2H), 2.51 (m, 2H), 2.41 (m, 1H), 1.71 (m, 8H), 1.20 (m, 4H); MS: *m/z* 169 (M^+), 152, 110 (base peak), 97, 69.

***trans*-*N*-(2′-Hydroxyethyl)-2-(*N*-pyrrolidinyl)cyclohexylamine (26)**—Methanesulfonyl chloride (0.95 mL, 12 mmol) was added in a dropwise manner to a stirred solution of 24 (1.01 g, 6 mmol) and triethylamine (1.67 mL, 12 mmol) in dry CH_2Cl_2 (20 mL) at 0 °C. After being stirred for 2 h, the reaction mixture was washed with H_2O (5 mL) and brine (5 mL), dried ($MgSO_4$), and evaporated to give 1.44 g of mesylate 25. Compound 25 and 2-aminoethanol (1.8 mL) were dissolved in THF (15 mL) and refluxed for 24 h. The mixture was concentrated under reduced pressure, 1 M $NaOH_{(aq)}$ was added, and the mixture was extracted with $CHCl_3$:isopropanol (4:1). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated to give 26 (1.27 g, 99%); IR (neat): 3600–3100 (br, OH & NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 4.12 (br, s, 2H), 3.52 (t, J = 5.8 Hz, 2H), 2.67 (m, 1H), 2.55–2.37 (m, 6H), 2.23 (m, 1H), 1.90 (m, 1H), 1.67–1.56 (m, 7H), and 1.11–1.01 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 61.72, 60.65, 59.32, 48.74, 46.68, 46.48, 31.35, 24.97, 24.46, 23.52, and 21.31; MS: *m/z* 213 (M^+), 84 (base peak).

***trans*-*N*-(2-Hydroxyethyl)-*N*-[2′-(*N*-pyrrolidinyl)cyclohexyl]phenylacetamide (22)**—Phenylacetyl chloride (6.68 mL, 50.5 mmol) was added in a dropwise manner to a stirred solution of 26 (4.9 g, 23 mmol) and triethylamine (8.02 mL, 57.5 mmol) in dry CH_2Cl_2 (100 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. Then, H_2O (10 mL) was added, and the organic layer was separated, washed with brine (10 mL), dried ($MgSO_4$), and concentrated by rotary evaporation. The residue was dissolved in methanol (15 mL) and treated with KOH (3 g), in H_2O (5 mL). After being stirred at room temperature for 20 min, methanol was removed by rotary evaporation and the mixture was extracted with CH_2Cl_2. The combined extracts were washed with brine, dried ($MgSO_4$), and concentrated to give a residue which was flash chromatographed (silica, 5–7% CH_3OH in CH_2Cl_2) to give 22 (7.17 g, 94%); IR (neat): 3600–3100 (OH), 1630 (s, CO) cm^{-1}; ^1H NMR (300 MHz, C_6D_6): δ 7.31–7.12 (m, 5H), 4.75 (br, s, 1H), 4.07 (m), 3.82–4.46 (m), 3.17 (br, 1H), 2.93–2.72 (m), 2.49 (br, s), 1.95–1.60 (m), and 1.34–1.05 (m); ^{13}C NMR (75 MHz, C_6D_6): δ 172.1 (171.7), 136.6, 129.3, 128.5, 126.9, 61.1 (61.0), 60.7, 59.4 (59.3), 46.6, 46.5, 42.2 (41.8), 32.1 (30.7), 25.8 (25.7), 25.2 (25.0), 24.0 (23.6), and 22.4 (NMR spectra are complicated due to the presence of *cis* and *trans* amides); MS: *m/z* 331 (M^+), 151 (base peak), 110, 91; HRMS: calc. for $C_{20}H_{30}N_2O_2$ (M^+), 330.2308; found, 330.2305.

Opiate Receptor Binding Assay—This was performed by the method of Tam.[15] Brain membranes were prepared from male Hartley guinea pigs. The following labeled ligands were used: 0.5 nM [^{3}H]naloxone (μ-binding); 1 nM (−)-[^{3}H]ethylketocyclazocine with 500 nM DADLE and 20 nM sufentanil (κ-binding); 0.7 nM [^{3}H]DADLE with 4 nM sufentanil (δ-binding). The IC_{50} values were calculated from log–logit plots. Apparent K_i values were calculated from the equation $K_i = IC_{50}/[1+(L/K_d)]$.

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16. Compound **19**: HRMS: *m/z* (M^+) calc. for $C_{21}H_{30}N_2OCl_2$, 396.1736; found 396.1724. *Anal.*—Calc. for $C_{21}H_{30}N_2OCl_2 \cdot HCl$: C, 58.14; H, 7.20; N, 6.46. Found: C, 57.64; H, 7.39; N, 6.29. Compound **20**: HRMS: *m/z* (M^+) calc. for $C_{21}H_{30}N_2O_2Cl_2$, 412.1685; found, 412.1682. *Anal.*—Calc. for $C_{21}H_{30}N_2O_2Cl_2 \cdot HCl$: C, 56.07; H, 6.95; N, 6.23. Found: C, 55.91; H, 6.79; N, 6.21. Compound **21**: HRMS: *m/z* (M^+) calc. for $C_{21}H_{32}N_2O_2$, 344.2464; found, 344.2463. *Anal.*—Calc. for $C_{21}H_{32}N_2O_2 \cdot HCl$: C, 66.21; H, 8.73; N, 7.35. Found: C, 65.93; H, 8.77; N, 7.09. Compound **22**: HRMS: *m/z* (M^+) calc. for $C_{19}H_{28}N_2O_2$, 316,2151; found, 316.2148. *Anal.*—Calc. for $C_{19}H_{28}N_2O_2$: C, 72.12; H, 8.92; N, 8.85. Found: C, 71.97; H, 8.74; N, 8.70.

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