constant, and t = incubation time in minutes.

Degree of Protection. Various concentrations of the *N*-allyl derivatives were added to 1.0 mL (0.5 unit) of BChE. After incubation for 3 min, 50 μL aliquots were assayed for enzyme activity. DFP (2.5×10^{-8} M) was added, and 50 μL aliquots were assayed for residual enzyme activity after various incubation times.

Affinity for the Muscarinic Receptor. Dissociation constants (K_D) of the complexes of the muscarinic receptor and the *N*-allyl derivatives were measured by two different procedures:

(a) Competition experiments used the S_1 supernatant fraction of mouse-brain homogenate.[14] Tritiated *N*-methyl-4-piperidyl benzilate ([^{3}H]-4NMPB) was incubated with the fraction of mouse-brain homogenate with and without the test compound in various concentrations. Nonspecific binding of the labeled ligand was determined,[14] and the difference in binding and the K_D value was calculated.

(b) Acetylcholine was added in a concentration at which 90% of the maximum contraction of the isolated guinea pig ileum was produced.[15] The compounds were tested as inhibitors of this contraction and dose–response curves were derived for calculation of K_D values from the dose ratios. The results by both methods were similar.

Mouse Platform Test. Male albino HAP ICR Swiss mice, 25–30 g, obtained from Harlan Sprague–Dawley Industries, Indianapolis, IN, were used for these experiments. The animals were housed in the rodent facility with a day–night cycle of 0700–1900 light and 1900–0700 dark and a room temperature of 21–25 °C. Food and water were supplied ad lib. and removed for the 3–4-h period the experiment. Experiments were performed between 0800 and 1200. The mouse platform was built to the specifications of Coughenour et al.[11] All mice were screened prior to use for passing the platform test. At 5, 15, 30, 60, 90, and 120 min after drug injection, the animals were placed, one mouse each, on a horizontal platform. The platforms were rotated 180° within 10 s and the mice scored on the basis of falling off the screen, failure to reach the top, and reaching the top of the screen during the period of 60 s. Gross behavior and the condition of the mice were observed within 3–4 h after injection. All compounds were administered ip with use of 0.9% NaCl as a vehicle in the form of a solution or a very fine suspension. In the case of a solubility problem of compound **7**, the suspensions were homogenized mechanically for 2 min with a glass Potter-Evelhejm homogenizer immediately prior to injection. Drug dosage was expressed in micromoles/kilogram. The volume of the dosing solution was 0.01 mL/g of body weight. The effect of the vehicle was checked in separate experiments. Four to six different doses of the same drug were tested daily. Six animals were used for each dose level. The experiments were replicated two to four additional times on different days. The quantal dose–response curves were determined graphically with use of all of the combined data obtained at the time of the peak effect. As described earlier, ED_{50} as well as 95% confidence limits were estimated from probit analysis using the Litchfield and Wilcoxon method.[12] For accurate dose–effect curves, 0% and/or 100% effects were corrected according to the method of Miller and Tainter[16] and Litchfield and Wilcoxon.[12]

Acute Toxicity Test. Compounds **4–6** were administered ip to groups of six male HAP ICR Swiss mice weighing 25–35 g. The LD_{50} values were estimated from the 1-day survivals of mice subjected to the behavioral screen. Deaths were determined 24-h postinjection. All quantal data were evaluated by the same method as the ED_{50}.

Interaction between PCP and the *N*-Allyl Derivatives. Male HAP ICR Swiss mice weighing 20–30 g were used under the same conditions as previously described. *N*-Allyl derivatives of PCA (**4–7**) were administered ip to groups of six mice at ED_{10} and ED_{20}. Five minutes later, PCP was administered ip at the dose close to ED_{50}. Then the same mouse platform tests were carried out as previously described.

Acknowledgment. This work was supported by Grant No. 1638 from the U.S.–Israel Binational Foundation and by NIDA Grant DA-01531 for which we express our appreciation.

Registry No. **1**, 2201-24-3; **2**, 2201-16-3; **4**, 2201-49-2; **4**·HCl, 2185-95-7; **5**, 91281-23-1; **5**·HCl, 91281-24-2; **6**, 82845-39-4; **6**·HCl, 91281-25-3; **7**, 91281-26-4; **7**·HCl, 91281-27-5; 11, 6289-40-3; **12**, 106-95-6; **13**, 91281-28-6; cyclohexanone, 108-94-1; methylamine hydrochloride, 593-51-1; phenyl bromide, 108-86-1; phenyllithium, 591-51-5; *N*-ethyl-1-phenylcyclohexylamine, 2201-15-2; butyrylcholinesterase, 9001-08-5; **2b**, 91281-35-5; **3b**, 91281-29-7; **3c**, 91281-32-2; **3d**, 91281-36-6; **4a**, 2014-75-7; **4a**·HCl, 34946-13-9; **4b**, 91281-31-1; **4b**·HCl, 91281-30-0; **4c**, 91281-34-4; **4c**·HCl, 91281-33-3; **4d**, 91281-38-8; **4d**·HCl, 91281-37-7; 2-methyl-2-oxazoline, 1120-64-5; 4-mercaptophenol, 637-89-8; ethyl iminoacetate hydrochloride, 2208-07-3; (±)-2-amino-1-propanol, 6168-72-5; dopamine β-hydroxylase, 9013-38-1; monamine oxidase, 9001-66-5.

Conformationally Restrained Fentanyl Analogues. 2. Synthesis and Analgetic Evaluation of Perhydro-1,6-naphthyridin-2-ones[1a]

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Conformational flexibility of the *N*-acyl portion of fentanyl-type analgetics was restricted through the synthesis of novel perhydro-1,6-naphthyridin-2-one derivatives. Neither the cis-fused derivative (**5a**), the trans-fused derivative (**5b**), nor the enamide **8a** possessed analgetic activity in the mouse tail-flick assay, reaffirming the sensitivity of this portion of 4-anilidopiperidine analgetics to conformational restraint.

Fentanyl (**1a**) is the most potent analgetic currently available (Sublimaze) in this country and has been the subject of a number of structural and conformational studies. Substitution of either the ethyl[2,3] or the phenyl[4] moiety on the propananilido group generally decreases activity, although an *o*-methoxy substituent appears to slightly increase opiate receptor binding.[5] A sharp reduction in binding affinity results from substitution of carbon for the amide nitrogen.[6] Although the *cis*-(+)-3-methyl analogue **1b** is reported to be 6684 times as potent as morphine,[7] a methyl group in the 2-position or 2,5-di-

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.

(1) (a) For paper 1, see: Borne, R. F.; Law, S. J.; Kapeghian, J. C.; Masten, L. W. *J. Pharm. Sci.* **1980**, *69*, 1104. (b) Abstracted in part from the Ph.D. dissertation of E.K.F.
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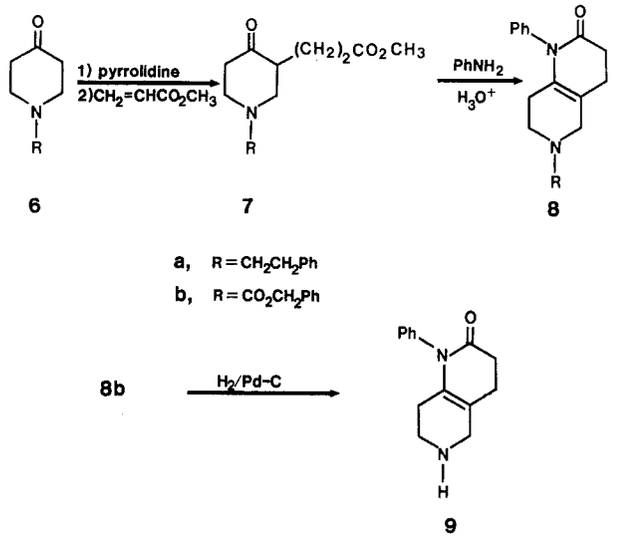
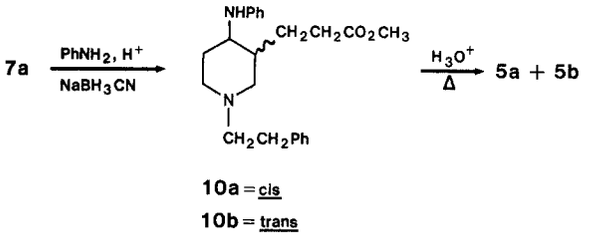
Scheme I



methylation leads to significant reduction in analgetic activity.[8] Substitution of a 4-methoxymethyl group leads to a compound possessing 10 000 times the potency of morphine in rats, while the corresponding thienylethyl analogue (sufentanil) is 2400 times as potent as morphine in dogs.[9] Introduction of alkoxycarbonyl or oxoalkyl substituents in the 4-position also enhances activity.[10] When the piperidine ring is either contracted to a 3-anilidopyrrolidine derivative[11] or expanded to a 4-anilidoperhydroazepine derivative[12] activity is decreased. Conformational factors have been less widely studied. Restriction of the piperidine to a chair-type conformation through the synthesis of tropane analogues of fentanyl[13] produced one isomer that was equipotent with fentanyl while restriction to a boat-type conformation through the synthesis of isoquinuclidine derivatives significantly decreases activity.[1a] Restriction of the *N*-phenethyl substituent to both syn and anti conformations within the same molecule also significantly diminishes activity.[14] Fusion of the propananilido group to the ortho position of the anilido phenyl ring produces the analogues **2** and **3**, which were found to lack analgetic activity.[15] Fusion of the ortho carbon atom of the aromatic ring to the 3-position of the piperidine ring to afford *cis*- and *trans*-hexahydropyrido[4,3-*b*]indoles **4** was reported to produce no activity.[16]

Scheme II



Intrigued by the apparent sensitivity of the fentanyl molecule to conformational restraint (in particular the *N*-acyl portion) and prompted by the pronounced analgetic activity of **1b**, we envisioned conformationally restricted analogues in which the 3-methyl substituent is connected to the propionyl side chain to give a series of perhydro-1,6-naphthyridine analogues as represented in **5a,b** (not taking into account the possibility of contributing half-chair conformations of the lactam ring). Because the cis-stereochemical relationship of **1b** is optimum for analgetic activity, it was postulated that the cis-isomer **5a** would possess greater analgetic activity than the trans-isomer **5b**. In this report we present the synthesis, proof of stereochemistry, and analgetic evaluation of **5a,b**.

Chemistry. A search of the literature for syntheses of the naphthyridine ring system revealed several methods for the preparation of 1,5- and 1,7-naphthyridines but fewer procedures for the 1,6-naphthyridine system. No methods for the preparation of the perhydro-1,6-naphthyridin-2-one system were found. The initial attempts to synthesize **5** are outlined in Scheme I. Treatment of the pyrrolidine enamine of **6a** with methyl acrylate afforded, after hydrolysis, the keto ester **7a**. Initial attempts to cyclize **7a** by refluxing (azeotropic) in toluene with aniline and either zinc chloride or *p*-toluenesulfonic acid were unsuccessful. Higher reaction temperatures were achieved by replacing toluene with xylene, but only starting material was again isolated. To determine if interaction between the lone pair of electrons on nitrogen and the carbonyl carbon decreased the reactivity of **7a** toward aniline, the phenethyl substituent was replaced by the less basic and readily removable carbobenzoxy group. Thus, **6b** was prepared by the method of Stetter and Reinartz[17] and **7b** in a manner similar to that used to prepare **7a**. When **7b** was refluxed in benzene with *p*-toluenesulfonic acid, the enamide **8b** was produced, although in low yield (14%). The three singlets of the enamide moiety in the carbon-13 NMR spectrum were particularly useful in supporting the structure of **8b**. Hydrogenolysis of **8b** with Pd/C proceeded only to cleave the carbamate **9** without reduction of the enamide double bond both in the presence and absence of acid. No reaction occurred when platinum oxide or rhodium on alumina was used as the catalyst. Reinvestigation of the cyclization of **7a** with aniline using 3A molecular sieves at 150 °C did result in the production of **8a**, but because initial attempts to reduce the enamide double bond were unsuccessful, the alternative route to **5a,b** outlined in Scheme II was explored. A modification of Borch's[18] reductive animation procedure was utilized to convert aniline and **7a** to a mixture of the two diastereomeric anilino esters **10a** and **10b**. Two isomers were isolated by column chromatography in a 3:7 ratio, which were subsequently determined to be the cis and trans diastereomers **10a** and **10b**. Because the preferred con-

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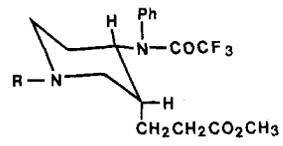
Table I. Analgetic Activity and Log *P* Values of Naphthyridine Analogues of Fentanyl

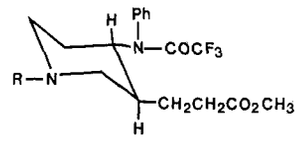
agonist[a]	ED_{50},[b] mg/kg	log *P*[c]	agonist[a]	ED_{50},[b] mg/kg	log *P*[c]
fentanyl citrate	0.010 (0.006–0.016)	2.63	5b·HCl	inactive at 100 mg/kg	2.50
5a·HCl	inactive at 100 mg/kg	2.59	8a·HCl	inactive at 75 mg/kg	2.68

[a] Subcutaneously, ICR Swiss male mice, normal saline vehicle. [b] Ninety-five percent confidence limits in parentheses. [c] By the method of Baker.[21]

formation of 3-substituted 4-anilidopiperidine is the chair form,[7] it was anticipated that stereochemical assignment could be based on the splitting pattern of the piperidine C-4 methine proton. However, in both cases this multiplet was masked by the large singlet of the methoxy group preventing assignment. Therefore, the anilino group of each individual isomer was trifluoroacetylated to give **11a** and **11b** in an effort to assign stereochemistry. Assuming



11a



11b

R = CH_2CH_2Ph

a chair conformation for the piperidine ring, the preferred conformer of the cis-isomer **11a** would most likely possess an equatorial trifluoroacetanilido group with the 3-substituent in the axial position, while the trans-isomer **11b** would have an equatorial 3-substituent. Indeed, this is supported by the NMR splitting pattern of the C-4 methine proton of the piperidine ring. The cis-isomer **11a** showed a multiplet at δ 4.07–4.45 consisting of a doublet (J = 11.4 Hz) of triplets (J = 4.8 Hz), while the trans-isomer **11b** exhibited a multiplet at δ 4.28–4.67 consisting of a triplet (J = 10.5 Hz) of doublets (J = 4.2 Hz). This is consistent with the spectra of the 3-methyl, 3-propyl, and 3-allyl analogues of fentanyl.[7,19] The relative stereochemistry of the 3- and 4-substituents of **10a** and **10b** was thus defined.

The diastereomeric mixture of **10a,b** was heated in 4 N hydrochloric acid to give a mixture of two products, each of which exhibited peaks at 1659 cm^{-1} corresponding to lactam absorption. Upon further analysis this mixture was determined to be the target naphthyridines **5a** and **5b**. Because the NMR spectra were not unambiguous, proof of stereochemistry was based upon conversion of pure **10a** and **10b** to **5a** and **5b**, respectively. However, certain NMR features of **5a,b** were supportive of the assigned stereochemistry. The C-8 methylene protons are shifted upfield by the anilido phenyl group in **5b**, whereas this is not possible in **5a**. Additionally, the C-8a methine proton in **5a** is downfield relative to **5b** due to deshielding by the anilido phenyl group.

Results and Discussion

Compounds **5a** and **5b**, as well as **8a**, were evaluated for analgetic activity subcutaneously in mice by using a modification of the D'Amour–Smith tail-flick assay.[20] Results are presented in Table I. None of the tested compounds except fentanyl elicited an analgetic response nor did the test animals exhibit a Straub-tail effect or display any observable behavioral changes at any dosage level employed. Log *P* values for the target compounds,

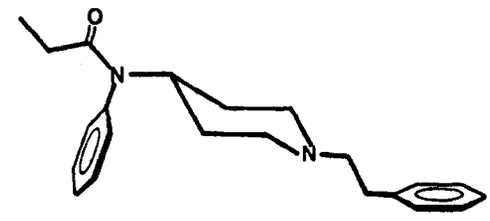


Figure 1. Conformation of fentanyl as suggested by X-ray and conformational energy analysis.[22,23]

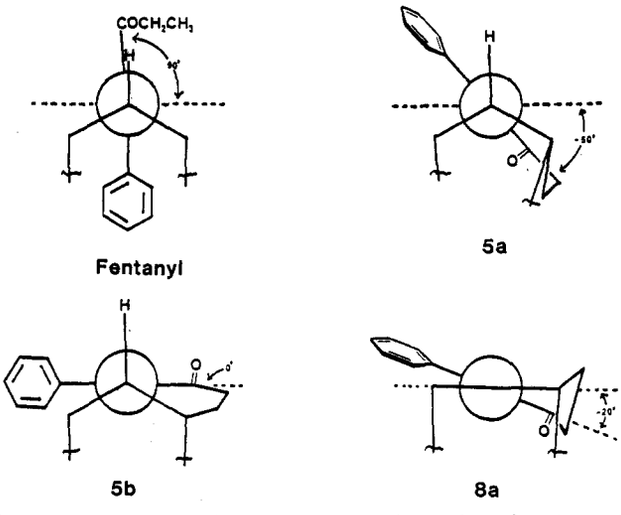


Figure 2. Projection diagrams of fentanyl, **5a**, **5b**, and **8a** (viewed along the C-4 atom of the piperidine ring and the anilido nitrogen bond using Dreiding models).

as well as for fentanyl, were determined by the method of Baker[21] and are also included in Table I. Because there was no significant difference in the values found for the test compounds from that of fentanyl, it may be assumed that the lack of activity is not due to an inability to penetrate into the CNS.

To date all reported attempts to restrict the propananilido side chain have led to compounds that lack analgetic activity. First-order ^1H NMR approximations of a series of N-substituted 4-anilidopiperidine derivatives and 3-methyl-4-propananilidopiperidines[7] imply that the preferred conformation is that of a piperidine chair with the 4-propananilido moiety in the equatorial orientation. Analysis of the crystal structures of fentanyl and its structural analogues indicate this is the case.[22,23] In addition, the *N*-phenethyl and propananilido moieties are extended in the crystal structure.[23] The amide function is planar and at a 90° angle to the mean plane of the piperidine ring. Also, the amide group is nearly perpendicular to the anilido phenyl group. The preferred conformation can be depicted as in Figure 1. Our compounds (**5a,b** and **8a**) like those previously mentioned (**2–4**) "freeze" the propananilido moiety in a conformation dif-

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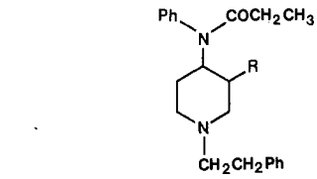
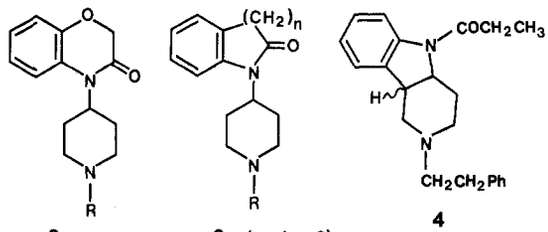
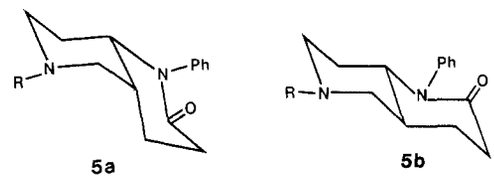


1a R=H
1b R=CH3



2 3 (n=1 or 2) 4

ferent from that of the solid-state conformation of fentanyl. If the pharmacophoric conformation is indeed the preferred crystalline conformation, it is clear in retrospect that neither **5a**, **5b**, nor **8a** (nor **2**–**4**) meet this requirement (see



5a 5b

Figure 2). Thus, one can conclude from this portion of the study that restriction of the propananilido side chain into the conformations shown in Figure 2 is apparently detrimental to analgetic activity. The 1,6-naphthyridine derivatives reported here and the restricted analogues discussed earlier (**2**–**4**) force the propananilido *N*-phenyl ring into a conformation other than that described above. The increased activity of the *cis*-3-methyl derivative **1b** compared to the corresponding trans isomer, and fentanyl, suggests that the axial 3-methyl substituent in **1b** may force the phenyl ring to assume this preferred conformation to avoid unfavorable interactions between the phenyl ring and the methyl group. Additionally, within a series of fentanyl analogues in which the propananilido *N*-phenyl ring is substituted with a methoxy group in either the ortho, meta, or para position,[5] the most active isomer was found to be the *o*-methoxy analogue. This suggests that the *o*-methoxy group may hinder rotation of the *N*-phenyl ring, thus altering the population of *N*-phenyl conformers (because of steric interactions with the axial hydrogen atoms at the 3-position of the piperidine ring) and "forcing" the ring to assume the preferred conformation. Studies are currently underway to test this hypothesis through the synthesis of analogues of fentanyl in which the propananilido function is restricted in the preferred solid-state conformation.

Experimental Section

All melting points were taken on a Thomas-Hoover Unimelt (uncorrected) or on a Mel-Temp apparatus. Infrared spectra were determined with a Perkin-Elmer Model 281B, a Perkin-Elmer Model 257, or a Beckman IR 33 spectrometer. Solution IR spectra were taken in matched sodium chloride cells of 0.197-mm (reference) and 0.214-mm (sample) widths. All ^1H NMR spectra were obtained on a Varian Model EM390 spectrometer, ^{13}C NMR spectra on a JEOLCO Model JNM-FX-60 Fourier transform spectometer, and all values are reported in ppm (δ) downfield from Me_4Si. Thin-layer chromatography was performed on Macherey-Nagel silica gel G (0.25 mm) with fluorescent indicator. Column chromatography was performed on Macherey-Nagel silica gel 60 (0.05–0.2 mm) and flash chromatography was performed on Merck silica gel 60 (0.040–0.063 mm) or on octadecyl C_{18}-Porasil reverse-phase packing. High-pressure liquid chromatographs were obtained on a Waters Associates HPLC unit equipped with a M-6000 pump, U5K or Rheodyne 7161 injector a Model 440 dual-wavelength UV detector (254 and 280 nm), and a μ-Bondapak ^{18}C reverse-phase column. Mass spectra and GC/MS were recorded at an electron energy of 70 eV on a Finnigan 3200, MS/DS system. Kugelrohr distillation implies bulb to bulb distillation and reported temperatures are oven temperatures, not actual boiling points. Elemental analyses were performed by either Galbraith Laboratories, Inc., Knoxville, TN, or Atlantic Microlab, Inc., Atlanta, GA.

3-(2-Carbomethoxyethyl)-1-(2-phenylethyl)-4-piperidone (7a). A solution of 20 g (0.096 mol) of **6a**,[24] 9.2 g (0.13 mol) of pyrrolidine, and 200 mL of anhydrous benzene was stirred at reflux under N_2 until no additional H_2O was collected. The solvent and excess pyrrolidine were removed in vacuo to yield 28 g of an orange oil. A solution of 24.6 g (0.096 mol) of the crude enamine, 18.8 g (0.192 mol) of methyl acrylate, and 200 mL of anhydrous benzene was refluxed under N_2 for 48 h. Water (75 mL) was added and the mixture refluxed for 2 h. The benzene layer was separated, dried over Na_2SO_4, and concentrated in vacuo to a yellow oil. Further purification was achieved by flash chromatography on silica gel 60 (Et_2O/benzene, 2:3) to give a yellow oil; picrate mp 150.5–151.5 °C. Anal. ($C_{17}H_{23}NO_3 \cdot C_6H_3N_3O_7$) C, H, N.

1-Phenyl-6-(2-phenylethyl)-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridin-2-one (8a). A solution of 2.0 g (6.9 mmol) of **7a**, 6.45 g (69 mole of aniline, a few crystals of *p*-toluenesulfonic acid, and 15 mL of anhydrous benzene, along with 10 g of 3A molecular sieves, was heated at 150° C in an autoclave for 72 h. The mixture was filtered, and the solvent was removed in vacuo to give a dark oil, which was Kugelrohr distilled [50 °C (0.2 mm)] to remove excess aniline. Thin-layer chromatography on silica gel G (EtOAc with 0.08% NH_4OH) indicated a major spot with R_f 0.21. Flash chromatography on silica gel 60 (same solvent) gave 260 mg of a dark solid. Analysis by HPLC (45%) MeOH in H_2O/^{18}C μ-Bondapak) indicated the presence of two components. Separation by reverse-phase flash chromatography (45% MeOH in H_2O/octadecyl Porasil) gave 105 mg (4%) of the desired enamide: IR ($CHCl_3$) 3001 (CH_2), 2929 (CH_2), 1663 cm^{-1} (C=O, enamide); ^1H NMR ($CDCl_3$) δ 1.73–1.98 (m, 2, NCH_2CH_2), 2.28 (br t, 2, CH_2CH_2C=O), 2.46–2.89 (m, 8, NCH_2, Ar CH_2CH_2C=O), 3.13 (br s, 2, NCH_2C=), 7.03–7.51 (m, 10, Ar H); MS, *m/e* 332.4 (M^+), 241.4 (base). The HCl salt was prepared and recrystallized from EtOH/Et_2O: mp 260–261 °C. Anal. ($C_{22}H_{24}N_2O \cdot {}^1/_2H_2O$) C, H, N (free base).

1-Carbobenzoxy-3-(2-carbomethoxyethyl)-4-piperidone (7b). A 300-mL round-bottom flask equipped with a Dean–Stark trap and reflux condenser was charged with 15.2 g (0.065 mol) of **6b**,[17] 6.93 g (0.098 mol) of pyrrolidine, and 175 mL of anhydrous benzene was refluxed under N_2 until no additional H_2O was collected (~18 h). The benzene and pyrrolidine were removed in vacuo to give the enamine as a yellow oil, which was then dissolved in 200 mL of anhydrous benzene, and 8.82 mL (8.43 g, 0.098 mol) of methyl acrylate was added. The mixture was refluxed under N_2 for 48 h and then 75 mL of H_2O was added and refluxing continued for 2 h. Upon cooling, the organic phase was removed and dried over Na_2SO_4. The solvent was removed in vacuo and the residual oil Kugelrohr distilled into two fractions. The fraction that distilled at 185–195 °C (0.2 mm) was the desired product. Anal. ($C_{17}H_{21}NO_5$) C, H, N.

6-Carbobenzoxy-1-phenyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridin-2-one (8b). A solution of 11.6 g (36.4 mmol) of **7b**, 10.1 g (109 mmol) of aniline, a few crystals of *p*-toluenesulfonic acid, and 75 mL of anhydrous toluene was placed in a 200-mL round-bottom flask equipped with a Dean–Stark trap and reflux condenser and refluxed for 24 h under N_2. After 0.6 mL of H_2O (92% of theory) was collected, the solvent was removed in vacuo to give an oil, which was taken up in 150 mL of Et_2O and extracted with cold 10% HCl (3 × 50 mL). The ether phase was dried over Na_2SO_4 and concentrated in vacuo to give 1.8 g (14%) of crude

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enamide. Flash chromatography of a 700-mg sample on silica gel 60 (EtOAc/PE 1:1) gave 600 mg of a yellow oil: IR ($CHCl_3$) 3008 (CH_2), 1700 (C=O, carbamate), 1670 cm^{-1} (C=O, enamide); ^{13}C NMR ($CDCl_3$) δ 169.2 (C=O), 131.0 (C-4 C=C), 110.8 (C-11 C=C). Anal. ($C_{22}H_{22}N_2O_3 \cdot {}^1/_4H_2O$) C, H, N.

1-Phenyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridin-2-one (9). A solution of 100 mg (0.28 mmol) of **8b**, 4 drops of concentrated HCl, and 25 mL of anhydrous EtOH was hydrogenated at 50 psi with 50 mg of 10% Pd-C for 20 h. The catalyst was removed by filtration through Celite and the filtrate was concentrated in vacuo to an oil. This was taken up in 20 mL of Et_2O, extracted with 5% HCl (2 × 15 mL), made basic with solid NaOH, and extracted with Et_2O (3 × 15 mL). After drying over K_2CO_3 and concentration in vacuo, 45 mg (71%) of an oily beige solid was obtained: IR ($CHCl_3$) 3000 (CH_2), 2903 (CH_2), 1671 (C=O, enamide), 1593 (Ar), 1492 cm^{-1} (Ar); ^1H NMR ($CDCl_3$) δ 1.55–1.80 (m, 2, NCH_2CH_2C=), 1.93 (br s, 1, NH), 2.23 (br t, 2, CH_2CH_2C=O), 2.55–2.80 (m, 2, CH_2C=O), 2.90 (br t, 2, CH_2CH_2N), 3.38 (br s, 2, NCH_2C=), 7.00–7.55 (m, 5, Ar H); MS, *m/e* 228.5 (M^+), 225.3 (base). A suitable salt form for elemental analysis was not obtained.

3-(2-Carbomethoxyethyl)-4-(phenylamino)-1-(2-phenylethyl)piperidine (10). A solution of 9.35 g (32 mmol) of **7a**, 18.1 g (194 mmol) of aniline, and 12.9 mL (2.34 g, 64 mmol) of 5 N HCl in MeOH in 125 mL of MeOH was stirred at room temperature while 1.22 g (19 mmol) of sodium cyanoborohydride was added followed by 45 g of 3A molecular sieves. This was stirred at room temperature for 3 days, filtered, cooled in an ice bath, and made acidic with concentrated HCl. The solvent was removed in vacuo, taken up in 150 mL of H_2O, and extracted with Et_2O (2 × 150 mL). The aqueous fraction was made basic with solid KOH, saturated with NaCl, and extracted with Et_2O (4 × 60 mL). The Et_2O fractions were dried over Na_2SO_4 and concentrated in vacuo to give a red oil. Kugelrohr distillation [60 °C (0.2 mm)] removed excess aniline and yielded 5.4 g (46% crude) of the diastereomeric products **10**. Column chromatography of 1.0 g of **10** on silica gel 60 [EtOAc (25%) and ammonium hydroxide (0.1%) in petroleum ether] gave 0.2 g of the isomer with R_f 0.42, which was subsequently shown to be the cis-isomer **10a**: IR ($CHCl_3$) 2950 (CH_2), 1725 (C=O, ester), 1600 (Ar), 1501 cm^{-1} (Ar); ^1H NMR ($CDCl_3$) δ 0.81–1.03 (m, 2), 1.14–1.40 (m, 2), 1.58–2.07 (m, 3), 2.07–2.97 (m, 9), 3.50–3.87 (m, overlapping s centered at 3.60, 4, OCH_3 and C-4 H), 6.53–6.78 (m, 3, ArH), 7.07–7.39 (m, 7, Ar H). Anal. ($C_{23}H_{30}N_2O_2$) C, H, N.

In addition to a fraction containing both isomers, a fraction containing 0.51 g of the isomer with R_f 0.32 was also obtained. This was subsequently proven to be the trans-isomer **10b**: IR ($CHCl_3$) 2953 (CH_2), 1724 (C=O, ester), 1601 (Ar), 1499 cm^{-1} (Ar); ^1H NMR ($CDCl_3$) δ 1.13–1.92 (m, 5), 1.92–2.48 (m, 5), 2.48–3.13 (m, 6), 3.50–3.69 (m overlapping s centered at 3.63, 4, OCH_3 and C-4 H), 6.50–6.77 (m, 3, Ar H), 7.05–7.34 (m, 3, Ar H). Anal. ($C_{23}H_{30}H_2O_2$) C, H, N.

1-Phenyl-6-(2-phenylethyl)perhydro-1,6-naphthyridin-2-one (5a,b). A mixture of **10a** and **10b** (4.7 g, 13 mmol) was heated at reflux for 20 h in 125 mL of 4 N HCl. The bulk of the solvent was removed in vacuo and the remainder was removed in a vacuum oven at 90 °C (20 mm) (24 h) to give 4.2 g (89%) of a tan solid, which TLC indicated to be a two-component mixture: IR ($CHCl_3$) 2960 (CH_2), 2360 (amine HCl), 1640–1650 cm^{-1} (C=O). Column chromatography of 1.0 g of the mixture on silica gel 60 (EtOAc with 1% NH_4OH) gave a fraction containing 220 mg of an oil, which solidified on standing (R_f 0.19), which was confirmed as the cis-isomer **5a** by conversion of pure **10a** to **5a** as described for the mixture: mp 102–103 °C; IR ($CHCl_3$) 3010 (CH_2), 2955 (CH_2), 1638 (C=O, amide), 1597 (Ar), 1497 cm^{-1} (Ar H); ^1H NMR ($CDCl_3$) δ 1.61–2.03 (m, 4), 2.22–3.05 (m, 11), 3.65 (m, 1, $CHNArC$=O), 7.10–7.49 (m, 10, Ar H); MS, *m/e* 335.5 (M + 1), 243.1 (base). The HCl salt was prepared in the normal manner, mp 196–198 °C (EtOH–Et_2O). Anal. ($C_{22}H_{26}N_2O$) C, H, N (free base).

In addition to a fraction containing both isomers, a fraction containing 450 mg of the trans-isomer **5b** (confirmed by conversion of pure **10b** to **5b** as described above) was obtained: mp 76–78 °C; IR ($CHCl_3$) 3005 (CH_2), 1638 cm^{-1} (C=O, amide); ^1H NMR ($CDCl_3$) δ 1.23–1.50 (m, 2, $NCHCH_2$), 1.65–2.09 (m, 5), 2.43–3.10 (m, 8), 3.20 (m, 1, NCH), 7.02–7.50 (m, 10, Ar H); MS, *m/e* 334.4 (M^+), 200.1 (base). The HCl salt was prepared in the normal manner, mp 293–295 °C (MeOH–Et_2O). The picrate salt was prepared and recrystallized from EtOH to give yellow crystals, mp 151.5–153 °C. Anal. ($C_{22}H_{26}N_2O \cdot C_6H_3N_3O_7$) C, H. N.

Pharmacology. Analgetic activity was evaluated by a modification of the D'Amour–Smith tail-flick method[20] using Swiss male albino mice (Madison Colony, 20–40 g; Harlan Industries, Inc., Cumberland, IN) and an analgesiometer as described by Bass and Vander Brook.[25] All drugs were injected subcutaneously. Fentanyl citrate (Sublimaze, Janssen Pharmaceutica) was used as a positive control. All standards and test compounds (as the HCl salts) were injected as normal saline solutions in a volume of 0.1–0.3 mL. Analgetic dose values (ED_{50}) and their 95% confidence limits were determined by the method of Litchfield and Wilcoxon.[26]

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Registry No. **5a**, 91157-46-9; **5a**·HCl, 91157-47-0; **5b**, 91157-48-1; **5b**·HCl, 91157-49-2; **5b** (picrate), 91157-50-5; **6a**, 39742-60-4; **6b**, 19099-93-5; **7a**, 91157-35-6; **7a** (picrate), 91157-37-8; **7b**, 91157-40-3; **8a**, 91157-38-9; **8a**·HCl, 91157-39-0; **8b**, 91157-42-5; **9**, 91157-43-6; **10a**, 91157-44-7; **10b**, 91157-45-8; pyrrolidine, 123-75-1; 1-(phenylethyl)-4-pyrrolidinyl-1,2,3,6-tetrahydropyridine, 91157-36-7; methyl acrylate, 96-33-3; aniline, 62-53-3; benzyl 4-pyrrolidinyl-1,2,3,6-tetrahydropyridine-1-carboxylate, 91157-41-4.

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