Investigation of the Synthesis and Analgesic Activity of 1-Substituted 4-(Propananilido)perhydroazepines

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Methods are explored to enhance the efficiency and versatility of the synthesis of the 1-substituted 4-(propananilido)perhydroazepine analgesics. The modified synthesis begins with ring expansion of 1-carbethoxy-4-piperidinone **3** with ethyl diazoacetate and boron trifluoride to yield 1,5-biscarbethoxyperhydroazepin-4-one **4**. Selective hydrolysis of **4** followed by decarboxylation provides 1-carbethoxyperhydroazepin-4-one **6**. Reductive amination of **6** with aniline affords the 4-anilino intermediate **7** which is treated with propionic anhydride to give 1-carbethoxy-4-(propananilido)perhydroazepine **18**. Selective cleavage of the 1-carbethoxy group of **18** was accomplished with trimethylsilyliodide to yield the versatile intermediate 4-(propananilido)-perhydroazepine **19**. Treatment of **19** with styrene oxide afforded the 1-[2-(1-hydroxy-1-phenyl)ethyl] derivative **1c** which, in the tail-flick assay, displays greater analgesic potential than previously reported members of this series.

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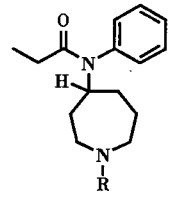
Results and Discussion.

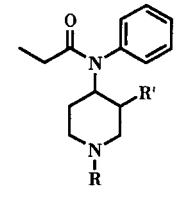
In an earlier publication we reported the synthesis of a number of 1-substituted 4-(propananilido)perhydroazepines **1** as ring expanded analogues of the 4-anilidopiperidine analgesics **2** [1]. In the mouse tail-flick assay, several of these compounds displayed analgesic potency comparable to the corresponding anilidopiperidines and morphine [1]. This impressive activity prompted the present study to develop improved methods for the synthesis of additional analogues of this novel class of analgesics.

The original approach employed for the synthesis of the perhydroazepines is outlined in Scheme 1. With this method, the 1-carbethoxy-4-perhydroazepinone **6** served as a key intermediate that was converted to a number of derivatives of **1** with varying substitutents at the 1-position. This intermediate was obtained from 1-carbethoxypiperidin-4-one **3** by the ring homologation method of Krogsgaard-Larsen and Hjeds [2] *via* treatment of **3** with ethyl diazoacetate in the presence of boron trifluoride etherate to provide the perhydroazepin-4-one-5-ester **4**. The undesired 5-ester moiety was then removed from the homologation intermediate **4** by acid-catalyzed hydrolysis followed by decarboxylation. During the course of this reaction, the 1-carbethoxy protecting group is also removed to yield **5**, and therefore N-1 reprotection was required prior

Figure 1

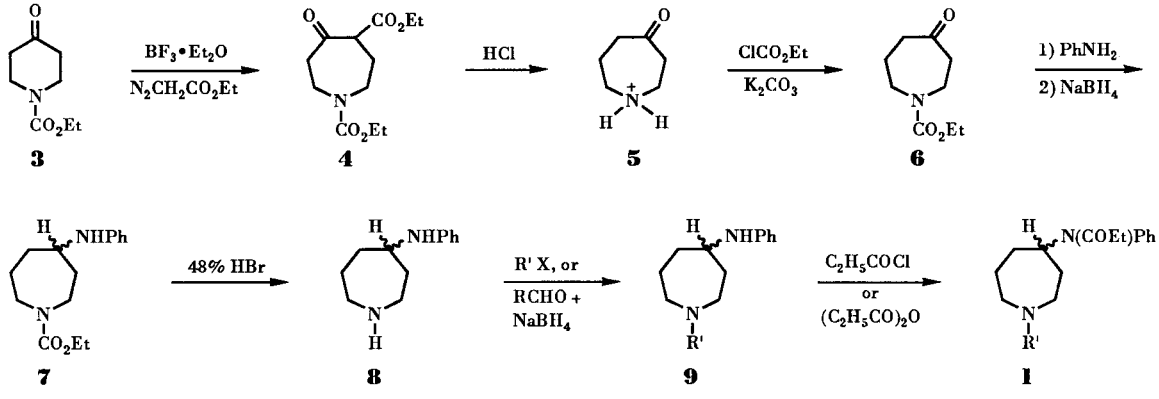


1a: R = -CH_2Ph
1b: R = -CH_2CH_2Ph
1c: R = -CH_2CH(OH)Ph



2a: R = -CH_2CH_2Ph, R' = H
2b: R = -CH_2CH(OH)Ph, R' = CH_3

Scheme 1



to continuation of the synthesis. Reprotection was accomplished by treatment of **5** with ethyl chloroformate in aqueous base to yield **6**.

The *N*-protected 4-perhydroazepinone **6** was then subjected to reductive amination by sequential treatment with aniline followed by reduction of the intermediate imine with sodium borohydride. The carbamate protecting group of the resultant 4-anilino intermediate **7** was then removed by acid-catalyzed hydrolysis (48% hydrobromic acid) to yield **8**. The varying N-1 substitutents were then introduced by either direct alkylation or reductive alkylation of **8**. Finally, propionylation of the 1-substituted 4-(anilino)perhydroazepine intermediates **9** afforded the desired analgesic derivatives **1** (Scheme 1).

While the method outlined in Scheme 1 was successfully employed to synthesize a number of 1-substituted-(4-propananilido)perhydroazepine analgesics, this approach is relatively inefficient. This is particularly true in the early stages of the synthesis where the ring expansion reaction also results in the incorporation of an undesired ester moiety **4**. The presence of this functionality added two additional synthetic transformations to the reaction sequence: 1) ester hydrolysis and decarboxylation, which was accompanied by decarbamylation, **5**, and 2) reprotection of the nitrogen atom before the synthesis could continue. The initial goal of the present study, therefore, was to investigate methods to form **6** directly from the starting piperidin-4-one **3**.

The first approach explored to accomplish this goal involved investigation of ring expansion reactions with diazomethane. Treatment of **3** with excess diazomethane (generated from Diazald®) in the presence of boron trifluoride etherate at $-25°$ to $-30°$ failed to yield the desired ring expansion product **6**. Repeating the reaction at higher temperatures ($-5°$) also did not result in formation of the perhydroazepine intermediate **6**; only unreacted **3** was isolated from these reaction mixtures. The failure of this reaction under these conditions may be related to decomposition of diazomethane by boron trifluoride as reported by Gutsche [3]. Therefore this expansion was investigated under conditions in which the Lewis acid was replaced by the protic solvent methanol [4]. Initial conditions employed for this reaction involved a 1.3:1 ratio of diazomethane (38.6 mmoles) to piperidinone **3** (29.2 mmoles) in 100 ml of methanol. Gas chromatographic-mass spectral (gc-ms) analysis of the product mixture resulting from this reaction revealed that it consisted of a mixture of three compounds in essentially equal quantities. The compound of shortest retention in the gc (4.6 minutes) was determined to be unreacted piperidinone **3** by gc-ms analysis of the starting material (Table 1). The compound of longest retention (5.4 minutes) had a mass of 185 and a fragmentation pattern identical with a standard sample of the desired perhydroazepinone **6** synthesized using the method outlined in Scheme 1 (Table 1). The third compound present in this reaction mixture had an intermediate retention (5.1 minutes) in the gc system and had a mass of 185. These data are consistent with the formation of either spiro-oxirane **10** or the aldehyde **11**. The formation of the spiro-oxirane could be rationalized by a mechanism involving nucleophilic attack of diazomethane on the piperidinone carbonyl, followed by displacement of nitrogen by the intermediate alkoxide (Scheme 2). The resultant spiro-oxirane could then undergo a ring-opening/hydride shift reaction to yield the aldehyde **11** [5]. Proton nmr evaluation of the crude product, however, did not reveal the presence of an aldehyde proton; the nmr spectrum did not contain any signals at fields lower than 5 ppm. An intense singlet at 2.8 ppm, however, was present in the spectrum. These nmr data suggested that the third

Scheme 2

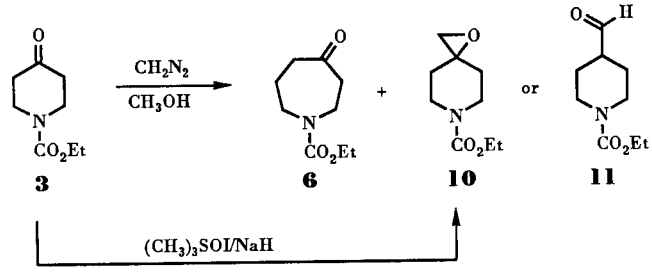


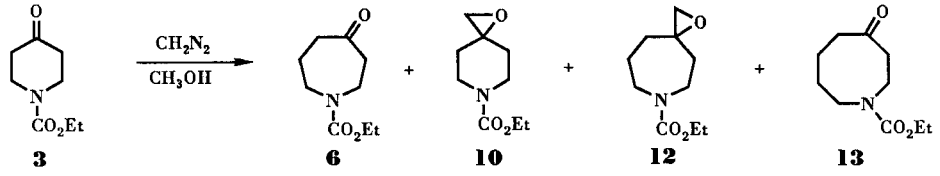
Table 1

Gas Chromatographic and Mass Spectral Fragmentation Data for Synthetic Standards

Compound	ret [a]	M+ [b]	m/z [c]					
			1	2	3	4	5	6
3	4.6	171	42	56	142	100	57	98
6	5.4	185	42	56	43	41	84	113
10	5.1	185	42	56	41	82	55	43
7	9.5	262	262	132	131	130	170	118
8	7.3	190	43	82	98	70	41	42

[a] Gas chromatographic retention times reported in minutes. [b] Molecular ion. [c] The six most abundant ions in the mass spectrum listed in order of highest relative abundance (1) to the sixth highest relative abundance (6).

Scheme 3



3 6 10 12 13

component present in this reaction mixture was not the aldehyde **11**, but rather the spirooxirane **10**. This speculation was confirmed by synthesis of **10** by an independent synthetic route involving treatment of piperidinone **3** with the ylide generated from trimethylsulfoxonium iodide (Scheme 2). The oxirane methylene protons gave a singlet integrating for two protons at 2.83 ppm and gc-ms analysis showed the spiro-oxirane had retention properties and a fragmentation pattern identical with the product obtained from the diazomethane homologation reaction (Table 1).

The results obtained from the first methanol-catalyzed ring expansion reaction described above clearly show that not all of the starting piperdinone **3** was consumed. Therefore this reaction was investigated further using a larger excess of diazomethane and increased methanol volume. The reaction conditions employed included a 2.1:1 ratio of diazomethane (38.6 mmoles) to piperidinone (18 mmoles) and 150 ml of methanol. Analysis (gc-ms) of the product mixture obtained from this reaction revealed the presence of four compounds. The presence of a very small gc peak with a retention of 4.6 minutes and a mass of 171 demonstrates that nearly all of the starting piperidinone **3** was consumed during this reaction. The presence of the desired perhydroazepinone **6** was indicated by a gc peak at 5.5 minutes with a mass of 185 and a fragmentation pattern consistent with the standard sample (Table 1). Also present in this mixture was the product of retention 5.1 minutes and a mass (185) and fragmentation pattern consistent with the proposed spiro-oxirane **10**. The third and fourth components in this mixture (retentions of 5.6 and 5.8 minutes) both had masses of 199 and fragmentation patterns consistent with the spiro-oxirane perhydroazepine derivative **12** and eight membered perhydroazocinone **13** resulting from a ring expansion of perhydroazepinone (Scheme 3). The structures proposed for these higher homologues were not confirmed independently. The results demonstrate that using approximately a two-fold excess of diazomethane in the ring expansion results in consumption of the starting piperdinone **3**, but also in the formation of the undesired higher homologues (mass of 199) presumed to be **12** and **13**.

Further study of the methanol-catalyzed diazomethane ring expansion of piperidinone **3** was targeted toward optimizing the yield of perhydroazepine **6** and minimizing the formation of undesired spiro-oxiranes **10** and **12**, and higher homologues such as **13**. At ratios of 1.7:1 of diazomethane to piperidinone all the starting heterocycle **3** was consumed, but the product mixture contained significant quantities of the spiro-oxirane **10** and perhydroazocinone **13**. These results suggest that it may not be possible to control this expansion reaction sufficiently to produce the desired perhydroazepinone **6** in high yield. Therefore an alternate strategy was explored involving modification of the original synthetic method (Scheme 1). In this approach, the perhydroazepin-4-one-5-ester **4** was synthesized as described earlier and methods were investigated to accomplish ester hydrolysis and decarboxylation without removal of the 1-carbethoxy protecting moiety.

Perhydroazepin-4-one-5-ester **4** was subjected to a variety of hydrolytic conditions in an effort to effect ester hydrolysis and decarboxylation. Base-catalyzed hydrolysis with 10% potassium carbonate at reflux was found to afford the perhydroazepinone **6** in excellent yield without hydrolysis of the 1-carbamate protecting moiety. Analysis (gc-ms) of the product obtained from this reaction revealed a major product with a retention time (5.4 minutes), mass (185) and fragmentation identical to a standard sample of **6** prepared by the original synthetic method. Several minor contaminants were also present. One was identified as the piperidinone **3** (retention of 4.6 minutes and mass of 171) which was carried through the sequence from the original ring expansion reaction (Table 1). The other product present in significant quantities was a higher homologue (mass of 199) presumed to the perhydroazocinone derivative **13**, which also appears to have originated during the initial ring expansion by homologation of the perhydroazepine ester **4**. Therefore careful hydrolysis of **4** in aqueous base affords the key perhydroazepinone **6** intermediate without deprotection of ring nitrogen moiety. Since the chromophoric beta-keto ester moiety of **4** has an intense absorption at 259 nm, while the product perhydroazepinone **6** has no uv absorbance above 220 nm, this hydrolysis reaction can be monitored by uv spectroscopy.

The ring expansion (Scheme 1) to afford the perhydroazepin-4-one-5-ester **4** was performed using a 1:1.32 ratio of **3** to ethyl diazoacetate and, as the hydrolysis studies above indicate, this ratio resulted in the formation of the higher homologue **13** and other contaminants. In an effort

to minimize the formation of such contaminants, this reaction was repeated using lower ratios of **3** to ethyl diazoacetate and the products analyzed following base-catalyzed hydrolysis and decarboxylation to yield **6**. The gc-ms analysis of this reaction demonstrated that with a 1:1.25 ratio of reactants, most of the starting piperidinone **3** (peak at 4.35 minutes) was consumed, and the desired perhydroazepinone intermediate **6** (peak 5.37 minutes and mass of 185) was obtained as the major product; again the structures of these products were confirmed by comparison to standards (Table 1). However, the product mixture also contained small quantities of the homologation product, again presumed to be the perhydroazocinone **13** and an unidentified high molecular weight contaminant. Also, further reduction of the ratio of **3** to ethyl diazoacetate (1:1) resulted in decreased yields of the desired perhydroazepin-4-one intermediate **6** and did not improve the ratio of **6** to higher homologue and other contaminants.

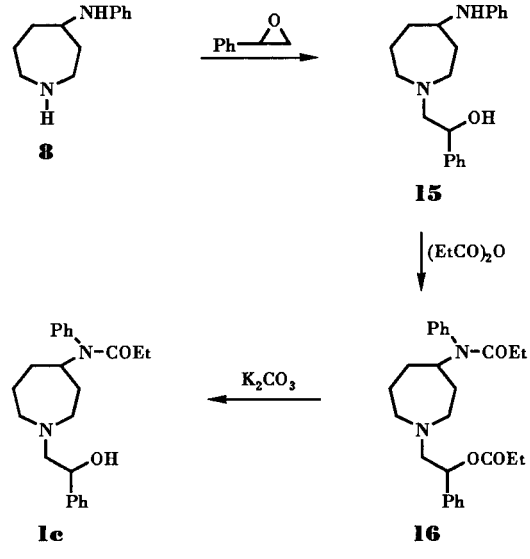
Formation of the 4-anilino intermediate **7** from the perhydroazepinone **6** prepared by selective hydrolysis was then investigated under varying reaction conditions. Reaction of **6** with aniline in the presence of a Lewis acid provides the corresponding imine which was isolated and reduced to the 4-anilino intermediate **7** with sodium borohydride [6]. The overall yield for this transformation ranged from 75 to 90%. This transformation was also accomplished directly by reductive amination of **6** using aniline in the presence of sodium cyanoborohydride. The latter method, while more efficient, afforded the 4-anilino intermediate **7** in lower yields (50 to 55%).

The next phase of the synthesis involved introduction of varying *N*-1-substituents. Therefore the 1-carbamate protecting group of **7** was removed by hydrobromic acid-catalyzed hydrolysis as described in the original synthesis. The resulting *N*-unsubstituted intermediate **8** was then purified by chromatography or vacuum distillation; the latter approach proved to be more efficient and convenient. Substituents such as simple alkyl or aralkyl groups were then incorporated by reductive amination. For example, treatment of **8** with benzaldehyde in the presence of sodium cyanoborohydride afforded the *N*-benzyl intermediate **9** in high yield.

Completion of the synthesis then required propionylation of the anilino nitrogen of **9**. In the original procedure [1] this transformation was accomplished by stirring mixtures of the 1-substituted intermediates **9** and propionic anhydride at reflux for several hours and then isolating the products by a series of acid-base extractions, followed by column chromatography. To enhance the efficiency of this portion of the synthesis, the propionylation was accomplished with a minimum amount of propionic anhydride in toluene and then washing the toluene solution with 30% potassium carbonate. This approach afforded the final products such as **1a** rapidly and in excellent yields.

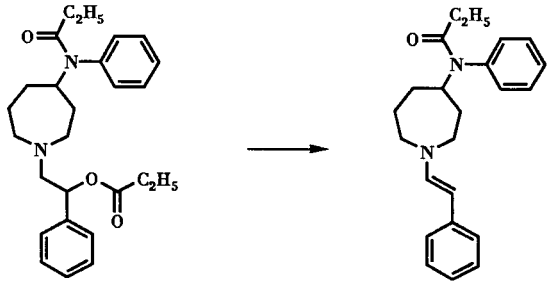
Recently Wenqiao *et al.* reported the synthesis and analgesic activity of the 1-[2-(1-hydroxy-1-phenyl)ethyl] derivative of cis-3-methylfentanyl **2b** [7]. In the mouse hot plate assay, **2b** is 28 times as potent as fentanyl and more than 6000 times as potent as morphine. These observations prompted the synthesis of the similarly 1-substituted-4-propananilido perhydroazepine derivative **1c**. The 1-[2-(1-hydroxy-1-phenyl)ethyl] moiety was introduced directly by treatment of **8** with styrene oxide, affording intermediate **15** in good yield (Scheme 4). To complete the synthesis of **1c**, propionylation of the anilino nitrogen was required. Treatment of intermediate **15** with propionic anhydride resulted in formation of the *N,O*-diacylation product **16** (Scheme 4). The structure of **16** is consistent with the presence of an amide (1640 cm^{-1}) and ester (1740 cm^{-1}) absorption in the infrared spectrum, and the presence of two sets of quartets (1.95 and 2.25 ppm) and triplets (1.00 and 1.10 ppm) in the proton nmr spectrum. Direct gc-ms analysis to establish the structure of **16** was complicated by the instability of this intermediate. In addition to a number of minor contaminants, the gc analysis revealed the presence of two major components, the most prominent (eluting at 19.3 minutes) had a molecular ion at 348, while the compound present in lower quantities (eluting at 19.8 minutes) had a mass of 422 consistent with the desired intermediate **16**. Since the compound present in larger quantities has a molecular ion (348) which is 74 mass units lower than the desired intermediate (422) product, it appears that this may represent the propionic acid elimination product **17**. This elimination product may have formed as a result of chemical decomposition prior to gc-ms analysis, or during the analysis due to the high temperatures required

Scheme 4



(Scheme 5). Either explanation seems plausible since intermediate **16** appeared to decompose readily upon standing.

Scheme 5

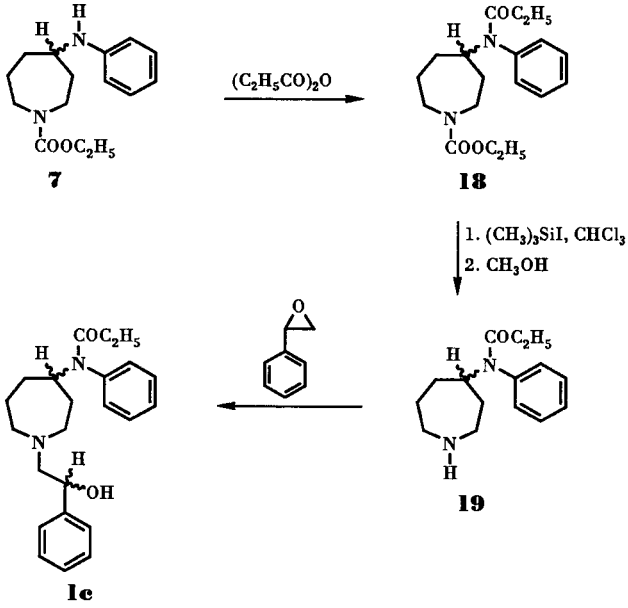


16 **17**

The desired 1-[2-(1-hydroxy-1-phenyl)ethyl] product **1c** was obtained by careful alkaline hydrolysis of the dipropionyl intermediate **16**. The structure of this product was confirmed by elemental analysis and spectroscopic methods. The ir spectra showed the loss of the ester carbonyl (1740 cm^{-1}) but retention of the amide carbonyl (1640 cm^{-1}). The proton nmr data revealed the presence of only a single quartet (1.95 ppm) and triplet (1.20 ppm). This structure and purity was also confirmed by gc-ms analysis which revealed the presence of one major component (18.4 minutes) with a mass of 366.

In an attempt to eliminate some of the difficulties encountered as a result of the formation of the unstable dipropionyl intermediate **16**, an alternate approach was examined involving incorporation of the 1-[2-(1-hydroxy-1-phenyl)ethyl] substitutent as the last step of the synthetic sequence. This was accomplished by the method outlined in Scheme 6 in which the anilino nitrogen of **7** was propionylated and methods were developed to decarbamoylate without hydrolysis of the propionamide **18**. Treatment of **18** with hydrogen bromide in acetic acid [8] or trimethylsilyl iodide followed by methanol [9] quenching afforded the 4-propananilidoperhydroazepine intermediate **19**. Reaction of **19** with styrene oxide then provided the desired **1c** product directly.

Scheme 6



7 **18** **19** **1c**

The potential analgesic activity of 1-[2-(1-hydroxy-1-phenyl)ethyl]-4-(propananilido)perhydroazepine product **1c** was evaluated by the mouse tail flick assay of D'Amour and Smith [10] and compared with 1-phenethylperhydroazepine derivative **1b**, morphine and fentanyl standards. In this assay **1c** has an ED_{50} of 0.13 mg/kg (Table 2) and therefore is 20 times as potent as morphine, but ten times less active than fentanyl. Comparison of the ED_{50} values for **1b** and **1c** reveals that the introduction of a *beta*-hydroxyl group on the phenethyl side chain of **1b** results in a 10 fold increase analgesic potency. Compound **1c** contains two chiral centers and since stereochemistry was not controlled in the synthesis, the compound evaluated exists as a mixture of four stereoisomers; evidence for the presence of diasteromers is clearly provided by proton nmr multiplicities for the methine protons. Since opiate receptors are capable of stereospecific recognition of ligands [11], it is reasonable that not all stereisomers of **1c** would display equal opiate receptor and analgesic potency. Therefore, it is possible that one or more stereoisomers of **1c** may possess analgesic potency significantly greater than that estimated by the ED_{50} value. Future studies will be directed toward the synthesis and analgesic evaluation of the individual isomers of **1c**, using the basic method reported here. This approach can be modified to allow for chiral induction at the imine reduction stage to afford the individual enantiomers of the 4-anilino intermediate **7**, and at the final stage by the use of individual styrene oxide enantimers. The modified synthesis may also be employed as a more direct method for the synthesis of other *N*-substituted 4-(propananilido)perhydroazepines since the decarbamoylated intermediate **19** can be directly alkylated to yield the final products.

Table 2
Analgesic Acivity

Compound	ED_{50}, mg/kg, sc (95% CL) [a]
Morphine Sulfate	2.2 (1.5-3.2)
Fentanyl Citrate	0.015 (0.013-0.018)
1b HCl	1.5 (0.9-2.6)
1c HCl	0.13 (0.071-0.25)

[a] Concentration required to produce analgesia in 50% of the test population in the tail-flick assay (95% confidence limits).

EXPERIMENTAL

Melting point were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were recorded with a Model 1600 Perkin Elmer Fourier Transform infrared spectrophotometer and ^{1}H nmr spectra were recorded on a Varian EM360 spectrometer with tetramethylsilane as an internal standard. The electron impact (ei) mass spectra were obtained using a Hewlett-Packard 5970B mass selective detector. The ionization voltage was 70 eV and the source temperature was 220°. The samples were dissolved in methanol (1 mg/ml) and 0.5 μl introduced into the mass spectrometer *via* a gas chromatograph equipped with a 12 m x 0.31 mm i.d. fused silica column with a 0.52 μm thickness of OV-1. The column temperature was programmed from 70° to 150° at a rate of 15°/minute and from 150° to 250° at a rate of 25°/minute. The split ratio for the gc was 10:1 and all samples eluted within 10 minutes. The gc retention data, molecular ions and six most abundant ions (in order of decreasing relative abundance) are reported for each compound below. These data for the synthetic standards are reported in Table 1. Common reagent grade chemicals were purchased from the Aldrich Chemical Company (Milwaukee, WI) and were used as received.

1,5-bis(Carbethoxy)perhydroazepine-4-one (**4**).

Solutions of boron trifluoride etherate (27.7 g, 187 mmoles) and ethyl diazoacetate (28.2 g, 247 mmoles), each in anhydrous ether (20 ml), were added simultaneously over 1.5 hours to a stirred solution of 1-carbethoxypiperidin-4-one (32.0 g, 187 mmoles) in anhydrous ether maintained at −25 to −30° (dry ice-2-propanol). After the additions were complete, the reaction mixture was maintained at −25 to −30° for 1 hour, and then allowed to warm to room temperature. The solution was washed with 30% potassium carbonate and the organic phase separated, dried over anhydrous potassium carbonate and concentrated *in vacuo* to give the intermediate perhydroazepine **4** (52.5 g) as an orange oil. This compound had spectral and physical properties identical to those reported earlier for **4** [1].

1-Carbethoxyperhydroazepin-4-one (**6**).

Method A.

The intermediate **4** was suspended in 4*N* hydrochloric acid (790 ml) and stirred at reflux for 6 hours. The resulting red solution was cooled to room temperature, concentrated *in vacuo* and dissolved in water (100 ml). The aqueous solution was cooled to −5° (methanol-ice) and 30% potassium carbonate (225 ml) added portionwise. Ethyl chloroformate (60 ml) was then added and the reaction mixture stirred at −5° for 4 hours. After warming to room temperature, the reaction mixture was extracted with ether (2 x 300 ml) and the combined ether extracts dried over anhydrous sodium sulfate. The ether solution was filtered, concentrated *in vacuo* and distilled to give **5** (17.6 g, 51%) as a clear oil, bp 0.25 mm 105-108°; gc-ms: 5.4 minutes, 185 (M^+), 42, 56, 43, 41, 112, 84. This compound had ir and nmr spectral and physical properties identical to those reported earlier for **6** [1].

Method B.

Diazomethane was generated *in situ* by addition of a solution of Diazald^R (12.16 g) in anhydrous ether (113 ml) to a stirred, heated (80-85°) solution of potassium hydroxide (2.8 g) in water (4.5 ml) and 95% ethanol (14.2 ml). The diazomethane generated was allowed to distill to a cooled (ice bath) receiving flask containing a stirred solution of **4** (5.0 g, 29.2 mmoles) in methanol (100 ml). After the addition of diazomethane was complete, the reaction mixture was stirred at room temperature for 20 hours, and then flushed with nitrogen gas. The mixture was then evaporated to dryness under reduced pressure to yield a pale yellow oil. The product mixtures obtained were analyzed by gc-ms and proton nmr and compared to standards (Method A and Table 1).

Method C.

The intermediate **4** (5.0 g, 19.5 mmoles), prepared as described above, and 10% potassium carbonate (50 ml) was stirred at reflux for 2 hours and then at room temperature for 15 hours. Dichloromethane (50 ml) was then added to the stirred solution, and the aqueous phase acidified (*p*H 1) by portionwise addition of concentrated hydrochloric acid. The dichloromethane phase was separated and the acidic aqueous phase extracted with an additional portion of dichloromethane (50 ml). The combined dichloromethane extracts were dried over anhydrous sodium sulfate, filtered and the filtrate solvent removed under reduced pressure. The resultant brown-yellow oil was distilled to obtain **6** as a clear oil, bp 4mm 135-140°. This compound had spectral and physical properties identical to those reported earlier for **6** [1].

Spiro-oxirane **10**.

Trimethylsulfoxonium iodide (2.9 g, 13 mmoles) was added portionwise to a suspension of sodium hydride (0.52 g of a 60% mineral oil dispersion, 13 mmoles) in dry tetrahydrofuran (100 ml). The reaction mixture was stirred at reflux for 1 hour, then cooled to room temperature. A solution of **3** (2.0 g, 12 mmoles) in tetrahydrofuran (50 ml) was then added dropwise and the reaction mixture stirred at reflux for 10 hours. After cooling to room temperature, the solvent was removed *in vacuo* and the residue suspended in ether (50 ml) and washed with water (50 ml).The ether solution was dried over sodium sulfate, filtered and the filtrate evaporated *in vacuo* to obtain **10** as a yellow oil; ^{1}H nmr (deuteriochloroform): 1.25-2.3 (m, 4H), 1.25 (t, 3H), 2.83 (s, 2H), 3.3-4.2 (m, 4H), 4.15 (q, 2H); gc-ms: 5.1 minutes, 185 (M^+), 42, 56, 41, 82, 55, 43.

1-(Carbethoxy)-4-anilinoperhydroazepine (**7**).

Method A.

A mixture of **6** (7.4 g, 40 mmoles), aniline (7.5 g, 81 mmoles) and zinc chloride (few crystals) in dry toluene (180 ml) was stirred at reflux for 15 hours. The water generated as a result of imine formation was removed using a Dean-Stark apparatus. The reaction mixture was cooled to room temperature, filtered and the filtrate evaporated under reduced pressure to yield an oil was which distilled *in vacuo* (0.5 to 1.0 mm) to remove unreacted aniline. The residue was treated with sodium borohydride (2.0 g, 53 mmoles) in methanol (100 ml) and stirred at reflux for 1 hour. The reaction mixture was cooled (room temperature), water (50 ml) added and evaporated *in vacuo* to yield a solid residue. This solid was extracted into toluene (2 x 30 ml) and the toluene dried over anhydrous magnesium sulfate. Filtration, followed by evaporation of the filtrate solvent yielded an oil (70-75% crude yield) which was distilled *in vacuo* to afford **7** as a clear oil, bp 0.75 mm 170-175°; ms: 262 (M^+), 262, 132, 131, 130, 170, 118. The ir and nmr data and physical properties were identical to those reported earlier for **7** [1].

Method B.

Sodium cyanoborohydride (11.3 g, 180 mmoles) was added portionwise to a stirred solution of **6** (11.0 g, 59.4 mmoles) and aniline (11.07 g, 119 mmoles) in acetonitrile (300 ml). Acetic acid (1 ml) was added and the reaction mixture stirred at room temperature for 24 hours. Additional acetic acid (0.5 ml) was added and the reaction mixture stirred for 48 hours at room temperature. The mixture was then evaporated to dryness and the resultant oil suspended in ether (500 ml). The ether solution was washed successively with 1*N* sodium hydroxide (200 ml), saturated sodium bicarbonate (200 ml) and water (300 ml), then dried over anhydrous sodium sulfate. Filtration, followed by evaporation of the filtrate solvent gave **7** as an orange oil (9.7 g, 62%). This compound had spectral and physical properties identical to those reported in Method A above.

4-Anilinoperhydroazepine (**8**).

A suspension of **7** (4.3 g, 16.4 mmoles) in 48% hydrobromic acid (50 ml) was stirred at reflux for 3 hours. The reaction mixture was then cooled to room temperature and made alkaline (*p*H 12) by addition of sodium hydroxide pellets. The resultant aqueous base suspension was extracted with ether (2 x 25 ml) and the ether extracts combined, dried over anhydrous potassium carbonate, filtered and the filtrate solvent removed under reduced pressure to yield an oil. Distillation of the oil afforded **8** (2.6 g, 85%) as a clear oil, bp 0.5 mm 130-133°; ms: 190 (M^+); 43, 82, 98, 70, 41, 42. The ir and nmr spectral data and physical properties were identical to those reported earlier for **8** [1].

1-Benzyl-4-anilinoperhydroazepine (**9a**).

Sodium cyanoborohydride (0.98 g, 15.8 mmoles) was added portionwise to a stirred solution of **8** (1.0 g, 5.25 mmoles) and benzaldehyde (0.65 g, 6.13 mmoles) in acetonitrile (30 ml) at room temperature. After the addition was complete, acetic acid (2 ml) was added and the reaction mixture stirred at room temperature for 6 hours. An additional portion of acetic acid (2 ml) was then added and the mixture stirred 30 hours. The acetonitrile solvent was then removed *in vacuo* and the resulting oil partitioned between ether (90 ml) and 1*N* sodium hydroxide (55 ml). After stirring for 1 hour at room temperature the two phases were separated and the ether solution washed successively with saturated sodium bicarbonate (70 ml) and water (70 ml). The product was then extracted into concentrated hydrochloric acid (50 ml) and the acid solution washed with dichloromethane (50 ml). The aqueous acid solution was then made basic (*p*H 12) with sodium hydroxide pellets and extracted with dichloromethane (3 x 50 ml). The combined dichloromethane extracts were washed with water (100 ml), dried over anhydrous magnesium sulfate, filtered and the filtrate evaporated under reduced pressure to yield **9a** as a brown oil. This compound had spectral and physical properties identical to those reported earlier for **9a** [1].

1-Benzyl-4-(propananilido)perhydroazepine (**1a**).

A solution of **9a** (1.00 g, 2.08 mmoles) and propionic anhydride (2.8 g, 22 mmoles) in toluene (35 ml) was stirred at reflux for 24 hours. The reaction mixture was then cooled to room temperature and washed with 30% potassium carbonate (35 ml). The toluene solution was dried over anhydrous magnesium sulfate, filtered and evaporated *in vacuo* to yield a yellow-brown oil. The unreacted propionic anhydride was removed by distillation at 100-120° (10 mm). This compound had spectral and physical properties identical to those reported earlier for **1a** [1].

1-[2-(1-Hydroxy-1-phenyl)ethyl]-4-anilinoperhydroazepine (**15**).

A solution of styrene oxide (0.6 ml, 4.8 mmoles) and **8** (0.826 g, 4.34 mmoles) in ethanol (100 ml) was stirred at room temperature for 18 hours. The reaction mixture was then evaporated *in vacuo* to yield a yellow oil that was dissolved in ether (50 ml) and extracted with 20% hydrochloric acid (2 x 25 ml). The hydrochloric acid extracts were combined and washed with ether (2 x 20 ml). The hydrochloric acid extracts were then made basic with saturated sodium hydroxide (*p*H 12) and extracted with ether (2 x 25 ml). The combined ether extracts were dried over anhydrous sodium sulfate, filtered, evaporated *in vacuo* to obtain **15** as a pale yellow oil (1.24 g, 92%). The dihydrochloride salt was prepared by treating **15** with ethereal hydrogen chloride; ^{1}H nmr (DMSO-d_6): 1.5-2.3 (m, 3H), 2.6-3.2 (m, 5H), 3.5-4.1 (m, 4H), 4.6-4.9 (d of d, 1H), 6.45-7.5 (m, 10H); ms: 310 (M^+), 146, 110, 209, 57, 47, 161.

Anal. Calcd. for $C_{20}H_{30}N_2O_2Cl_2$: C, 59.85; H, 7.53; N, 6.98. Found: C, 59.99; H, 7.76; N, 6.90.

1-[2-(1-Propoxy-1-phenyl)ethyl]-4-(propananilido)perhydroazepine (**16**).

A solution of **15** (3.41 g, 11 mmoles) in benzene (75 ml) was stirred at reflux in the presence of propionic anhydride (22 ml) for 10 hours. The reaction mixture was allowed to cool to room temperature and concentrated *in vacuo* to obtain a brownish-yellow oil which was stirred in saturated sodium bicarbonate solution (150 ml) at 50° for 3 hours. The solution was allowed to cool to room temperature and extracted with ether (4 x 25 ml). The combined ether extracts were dried over anhydrous magnesium sulfate, filtered and the filtrate evaporated *in vacuo* to obtain **16** as a yellow oil (2.7 g, 59%); ir (film): 1650 (amide C=O) and 1738 (ester C=O); ^{1}H nmr (deuteriochloroform): 0.95-1.3 (m, 6H), 1.4-2.5 (m, 10H), 2.5-3.0 (m, 6H), 4.4-5.0 (br m, 1H), 5.7-6.0 (br m, 1H), 7.0-7.5 (m, 10H); ms: 422 (M^+), 335, 186, 57, 96, 92, 145.

1-[2-(1-Hydroxy-1-phenyl)ethyl]-4-(propananilido)perhydroazepine (**1c**).

Method A.

A solution of **16** (0.70 g, 1.7 mmoles) in a mixture of ethanol (10 ml) and 30% potassium carbonate (25 ml) was stirred at 60-70° for 10 hours. The reaction mixture was cooled to room temperature and the ethanol evaporated *in vacuo*. The remaining aqueous suspension was extracted with ether (2 x 25 ml) and the combined ether extract dried over anhydrous magnesium sulfate, filtered and the filtrate solvent evaporated *in vacuo* to yield **1c** as a viscous yellow oil (0.50 g, 82%). The product obtained by this method has spectral properties identical to **1c** obtained by Method B.

Method B.

Styrene oxide (0.216 g, 1.57 mmoles) was added to a solution of **19** (0.30 g, 1.25 mmoles) in ethanol (10 ml) and this solution was stirred at room temperature for 18 hours. The reaction mixture was then evaporated under reduced pressure and the resulting oil suspended in ether (50 ml) and filtered. The ether filtrate was extracted with 20% hydrochloric acid (2 x 25 ml) and the combined acid extracts made basic (*p*H 12) with saturated sodium hydroxide. The aqueous base solution was extracted with ether (2 x 25 ml) and the combined ether extracts dried over sodium sulfate, filtered and evaporated under reduced pressure to yield the **1c** as a pale yellow oil (0.23 g, 88%); ir (film): 3416 (OH), 1650

(amide C=O); ^{1}H nmr (deuteriochloroform): 1.0 (t, 3H), 1.4-2.35 (m, 8H), 2.5-3.2 (m, 6H), 3.5-4.1 (m, 2H), 4.5-5.0 (m, 1H), 7.0-7.7 (m, 10H); ms: 366 (M^+), 110, 259, 146, 355, 142, 42. Treatment of **1c** with ethereal hydrogen chloride afforded the hydrochloride salt which was recrystallized from ether-2-propanol, mp 200° dec.

Anal. Calcd. for $C_{23}H_{31}N_2O_2Cl \cdot 0.33H_2O$: C, 67.56; H, 7.81; N, 6.85. Found: C, 67.57; H, 7.89, N, 6.72.

1-Carbethoxy-4-(propananilido)perhydroazepine (**18**).

A solution of **7** (0.69 g, 2.64 mmoles) in benzene (10 ml) was allowed to stir at reflux in the presence of propionic anhydride (2.7 ml) for 18 hours. The solution was cooled to room temperature and the solvent evaporated *in vacuo*. Saturated sodium bicarbonate (50 ml) was added and the suspension stirred at 50° for 3 hours. After cooling to room temperature, the reaction mixture was extracted with ether (2 x 25 ml) and the combined ether extracts dried (sodium sulfate), filtered and the filtrate solvent evaporated *in vacuo* to yield **18** as a pale yellow oil (0.82 g, 97%); ir (film): 1691 (carbamate C=O), 1650 (amide C=O); ^{1}H nmr (deuteriochloroform): 1.0-1.4 (m, 6H), 1.5-2.5 (m, 8H), 3.1-3.8 (m, 4H), 4.15 (q, 2H), 4.4-5.0 (br m, 1H), 7.0-7.6 (m, 5H); ms: 318 (M^+), 57, 132, 93, 149, 43, 170.

4-(Propananilido)perhydroazepine (**19**).

Method A.

Trimethylsilyl iodide (0.33 g, 1.23 mmoles) was added to a solution of **18** in chloroform (0.5 ml) and the reaction mixture stirred at reflux under nitrogen for 3 hours. The reaction mixture was then cooled to room temperature and methanol (5 ml) added. After stirring for 30 minutes, the reaction mixture was evaporated *in vacuo* and the residue suspended in 2*N* hydrochloric acid (30 ml) and extracted with ether (4 x 20 ml). The acidic solution was made basic upon addition of saturated sodium hydroxide (*p*H 12) and extracted with ether (2 x 25 ml). The combined ether extracts were dried over sodium sulfate, filtered and evaporated under reduced pressure to obtain **19** as a pale yellow oil (0.15 g, 58%); ir (film): 1650 (amide C=O), 3340 (NH). ^{1}H nmr (deuteriochloroform): 1.1 (t, 3H), 1.5-2.3 (m, 8H), 2.5-3.2 (m, 4H), 3.6-4.0 (m, 1H), 7.1-7.6 (m, 5H); ms: 246 (M^+), 97, 82, 57, 41, 43, 44.

Method B.

A solution of **18** in 33% hydrobromic acid in acetic acid (5.0 ml) was stirred for 18 hours at room temperature. The reaction mixture was basified with saturated potassium carbonate (*p*H 10) and extracted with ether (2 x 25 ml). The combined ether extracts were dried over sodium sulfate, filtered and evaporated under reduced pressure to yield **19** as a pale yellow oil (0.18 g, 26%). The product obtained by this method has identical spectral properties to **19** obtained by Method A.

Pharmacology.

The test compound **1c** was evaluated as a saline solution of the hydrochloride salt using a modification of the D'Amour-Smith tail-flick analgesic assay [10]. The analgesic activities of morphine sulfate and fentanyl citrate were determined as standards. Male albino ICR mice weighing 30-40 g were given thermal stimulus challenge 20 minutes post-injection (subcutaneous) of the test compound and standards using an Emdie analgesiometer. Each group of mice served as its own control and the threshold response time for positive analgesia was determined for each group. Positive analgesia was defined as a tail-flick response time greater than or equal to the mean response time of the control plus two standard deviations of their mean. Median analgesic doses (ED_{50} values) and their 95% confidence limits were determined by the method of Litchfield and Wilcoxon [12] and are presented in Table 2.

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