Synthesis and Analgetic Activity of Some Benzomorphan Analogues

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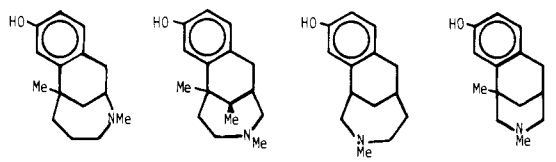
The benzomorphan analogues, 8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (1), 8-hydroxy-2-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-2-benzazepine (2), 9-hydroxy-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine (3), and 10-hydroxy-2-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine (4), have been synthesized in order to evaluate their analgetic activity. Only slight analgetic activity was found in any of these compounds. The importance of nitrogen to aromatic ring distance for the analgetic–receptor interaction is discussed.

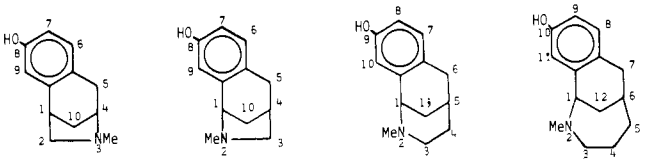
Chemical modifications by altering the substituents at several positions of 2-methyl-6,7-benzomorphan have been intensively studied, and these modifications have led to the discovery of a considerable number of compounds possessing interesting profiles with respect to analgetic and narcotic antagonist activity.[1] Modification of the benzomorphan skeleton itself, however, has attracted only limited attention. Jacobson and Mokotoff have synsthesized *B*-norbenzomorphan.[2] May and co-workers have prepared 3-benzazocine derivatives where the methano bridge of 6,7-benzomorphan is removed in order to determine the role of the methano bridge for analgetic activity.[3] Takeda and co-workers have modified the skeleton by shifting the C_2–N bond to C_{11}–N.[4] These modifications have decreased analgetic activity. Montzka and Matiskella have introduced a methylene group to connect the 1 and 4 positions of 6,7-benzomorphan. This modification has produced compounds with interesting narcotic antagonist and analgetic activity.[5] Analogously, indeno[2,1-*c*]pyridine and its 1,3-ethano derivatives[6] and 1,5-ethano-1*H*-3-benzazepine derivatives[7] have been synthesized, which have been reported to be almost inactive as analgetics. Recently, Cavestri and Mokotoff have synthesized 2-azabicyclo[3.3.1]nonene derivatives, in order to test the necessity of the aromatic ring for analgetic activity; no significant activity was found for these compounds.

In order to investigate further the structure–activity relationships of the compounds having a fixed axial conformation of the aromatic ring for the nitrogen-containing ring, we have undertaken modifications of benzomorphan by changing the position of nitrogen, enlarging the size of the C ring, and reducing the size of the C ring. We have, along this line, already reported the synthesis and analgetic activity of derivatives of 2,3,4,5,6,7-hexahydro-2,7-methano-1*H*-3-benzazonine (I),[9] 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-4-benzazonine (II),[9,10] 2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-3-benzazonine (III),[11] and 1,2,3,4,5,6-hexahydro-1,5-methano-3-benzazocine (IV).[12,13]



I II III IV

Takeda and co-workers have also synthesized derivatives of I by a novel rearrangement.[14] Some derivatives of I and II have been shown to be analgetically as potent as morphine and those of III and IV as potent as codeine.[10-12,14] These modifications should affect the steric environment around the nitrogen and above the aromatic ring. Several workers have proposed that this steric environment may be important for binding on the receptor site.[15-22] We also have proposed the importance of the distance between the nitrogen and aromatic ring for analgetic activity.[23] Therefore, it appeared interesting to synthesize some other compounds having a fixed axial conformation of the aromatic ring for the nitrogen-containing ring and to evaluate the analgetic activity. In this paper we describe the synthesis of 8-hydroxy-3-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (1),

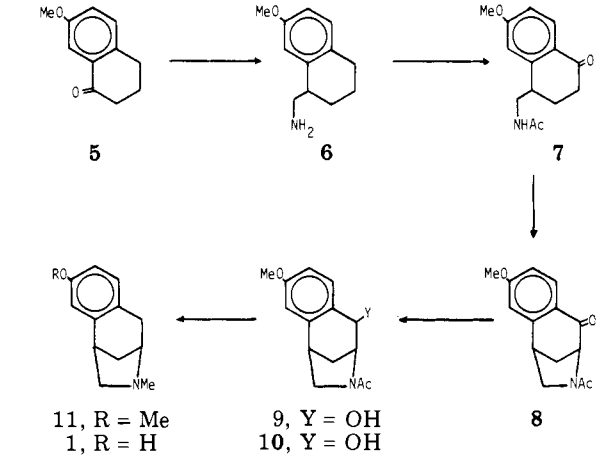


1 2 3 4

8-hydroxy-2-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-2-benzazepine (2), 9-hydroxy-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine (3), and 10-hydroxy-2-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine (4) and their analgetic activity.

Chemistry. Previously we have reported the synthesis of compound 1 via nitration of the deoxy compounds and separation of the resulting isomeric nitro derivatives.[13] Because the sequence was thought to be tedious, in this paper we report an alternative route. 1-Aminomethyl-7-methoxytetralin (6), prepared from 7-methoxy-α-tetralone (5) by the method reported in our previous paper,[11] was *N*-acetylated, followed by oxidation with $Na_2Cr_2O_7$ in dilute sulfuric acid to give 4-acetamidomethyl-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (7) in good yield. Conversion of 7 into the 1,4-methano-1*H*-3-benzazepine derivative 8 was effected by bromination to give the 2-bromo compound, followed by treatment with NaOMe.[24] The oxo compound 8 was reduced with $NaBH_4$, followed by catalytic hydrogenation over Pd/C to afford compound 10. The *N*-acetyl group was hydrolyzed, and the resulting secondary amine was methylated with HCOOH–HCHO to give the *N*-methyl derivatives 11. O-Demethylation of

Scheme I



5 6 7 8

11, R = Me
1, R = H

9, Y = OH
10, Y = OH

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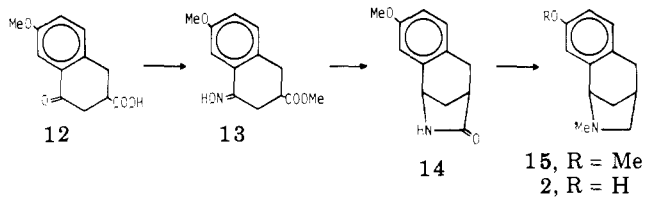
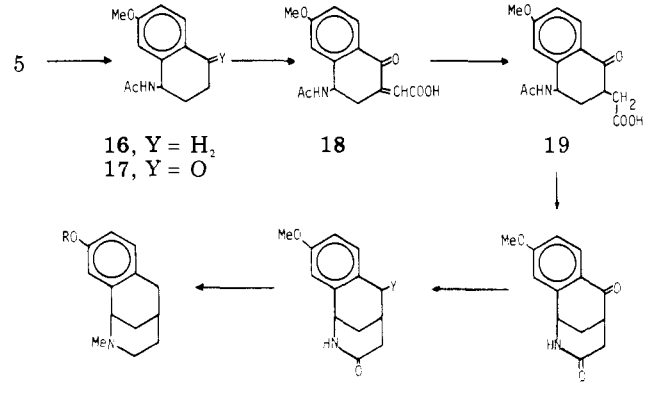
Scheme II



12 13 14 15, R = Me; 2, R = H

Scheme III



16, Y = H_2; 17, Y = O 18 19 20 21, Y = OH; 22, Y = H 23, R = Me; 3, R = H

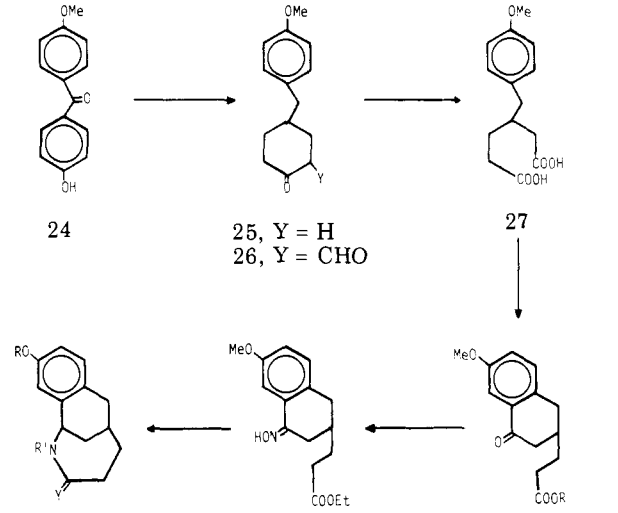
11 by refluxing with hydrobromic acid afforded the final product 1 (Scheme I).

The synthesis of compound 2 was achieved by the reactions shown in Scheme II. Esterification and the subsequent oximation of keto acid 12[25] afforded oxime 13. Compound 13 was hydrogenated over Pt in AcOH–MeOH to give the amino ester derivative, which readily underwent cyclization to lactam 14 upon standing for several hours at room temperature. Though it would be expected that hydrogenation of 13 would produce a stereoisomeric mixture of 1,3-disubstituted tetralins, the good yield of lactam 14 would suggest predominant formation of the cis isomer.[26] Reduction of the lactam with $LiAlH_4$ gave the corresponding amine 15. Treatment of 15 with hydrobromic acid under refluxing gave the O-demethylated compound 2.

The 1,5-methano-2-benzazocine compound 3 was synthesized by the reactions shown in Scheme III. The oxime of 7-methoxy-α-tetralone (5) was hydrogenated over Pt, followed by acetylation to give 1-acetamidotetralin (16). Oxidation of 16 with $Na_2Cr_2O_7$ gave ketone 17. Condensation of 17 with glyoxylic acid[27] gave an α,β-unsaturated carboxylic acid 18. On hydrogenating over Pt in MeOH the C=C bond was easily reduced to give saturated keto acid 19. Although a stereoisomeric mixture of 2,4-disubstituted α-tetralone would be anticipated, no attempt was made to separate them because only the cis isomer would cyclize to form lactam 20.[11] Hydrolysis of the *N*-acetyl group and esterification of the carboxyl group in the presence of H_2SO_4 gave an amino ester salt, which, on basifying, afforded the desired keto lactam 20 immediately. Reduction of 20 with $NaBH_4$ gave the hydroxyl derivative 21. The hydroxyl group of 21 was hydrogenolyzed over Pd/C in AcOH–$HClO_4$ to yield lactam 22. Compound 22 was reduced with $LiAlH_4$, followed by N-methylation with HCOOH–HCHO, to give amine 23, from which the 9-hydroxy derivative 3 was obtained by refluxing with hydrobromic acid.

The synthesis of the 1,6-methano-1*H*-2-benzazonine compound 4 was accomplished by the sequence shown in Scheme IV. Wolff–Kishner reduction of 4-(*p*-methoxy-

Scheme IV



24 25, Y = H; 26, Y = CHO 27 28, R = H; 29, R = Et 30 31, R = Me, R′ = H, Y = O; 32, R = Me, R′ = Me, Y = H_2; 4, R = H, R′ = Me, Y = H_2

benzoyl)phenol (24)[28] and the subsequent reduction over Raney nickel at 110 kg/cm^2 and 120–140 °C gave 4-(*p*-methoxybenzyl)cyclohexanol. Oxidation of the cyclohexanol derivative with $Na_2Cr_2O_7$ yielded the cyclohexanone derivative 25. Condensation of 25 with HCOOEt in the presence of NaH gave the unstable α-formyl ketone 26. Compound 26 was oxidized with H_2O_2 in alkaline solution to give diacid 27. Cyclization of 27 with PPA gave 4-oxo-6-methoxy-1,2,3,4-tetrahydronaphthalene-2-propionic acid (28). The ethyl ester (29) of 28 was oximated to give compound 30. Hydrogenation of the oximino group over Pt and cyclization by heating at 200 °C afforded the desired lactam 31. In this case also, the hydrogenation of oxime 30 would give a stereoisomeric mixture of 1,3-disubstituted tetralins. No attempt was made to separate the isomers because only the cis isomer would cyclize to give 31.[11] Lactam 31 was reduced with $LiAlH_4$, followed by N-methylation with HCOOH–HCHO, to give compound 32. O-Demethylation of 32 by refluxing with hydrobromic acid gave the final compound 4.

Pharmacology. The analgetic activities of the compounds described here were determined by the method of pressure stimuli on the mouse tail[29] after sc administration; groups of ten albino male mice dd strain were tested at five dose levels. ED_{50} values were calculated from the pain reaction by the Lichfield–Wilcoxon method.[30] The results of the test of compounds described here and in ref 10–12 and 14 are summarized in Table I. Based on the data, compounds 1–4, III, and IV are very weak as analgetics, though all of these have the phenolic hydroxyl group which distinctly enhances analgetic activity of 6,7-benzomorphans.[1] It is noteworthy that structural modifications of 6,7-benzomorphan by changing the position of nitrogen, enlarging the size of the C ring, or reducing the size of the C ring decrease the analgetic activity, except for structures I and II.

Since the importance of the nitrogen to phenyl distance (N–Ph distance) in structure–analgetic activity relationships has been described recently,[15-23] it is worth noting the correlation of the N–Ph distance and activity of these benzomorphan analogues. Table I also shows the results of calculations of the N–Ph distance. The values of I, II, IV, and 6,7-benzomorphan were deduced from the atomic

Table I. Analgetic Activities and Nitrogen to Aromatic Ring (N-Ph) Distances of Benzomorphan Analogues

compd	ED_{50}, mg/kg sc[a] (95% SE limits)	N-Ph distance,[b] Å
1·HBr[c]	43.0 (27.8-66.4)	(4.17)
2[d]	29.1 (18.5-45.8)	(3.75)
3[c]	17.2 (10.5-28.1)	(3.75)
4·HCl·H_2O	15.0 (11.5-19.5)	(3.75)
I·HBr	4.1 (3.1-5.1)[e]	4.45
II·HBr[f]	1.0 (0.86-1.16)	4.87
III·HBr[g]	38.8 (28.1-53.5)	(4.10)
IV·HBr[h]	8.4 (7.2-9.9)	4.11
2-Me-2'-OH-6,7-benzomorphan	4.5[i]	4.69
morphine[j]	1.2 (1.0-1.5)	
codeine[k]	9.2 (8.1-10.4)	

[a] Mouse tail pressure stimuli method. [b] Average N-C distance to the six atoms of the benzene ring. The figures in parentheses are estimated values; see text. See also ref 23. [c] Administered in saline. [d] Administered as lactate in saline. [e] See ref 14. [f] See ref 10. [g] See ref 11. [h] See ref 12. [i] Data from K. Kanematsu, M. Takeda, A. E. Jacobson, and E. L. May, *J. Med. Chem.*, 12, 405 (1969). The figure actually given here was obtained by the mouse hot-plate method. [j] Administered as the hydrochloride in saline. [k] Administered as phosphate in saline.

coordinates from the crystal-structure data of these compounds as described in our previous paper.[23] The values for 1 and 2 were estimated from the atomic coordinates of *N*-methyl-*D*-normorphinan,[31] that for 3 from the atomic coordinates of 6,7-benzomorphan[32] and IV,[33] and those for 4 and III from the atomic coordinates of I and II[33] by assuming that the structures of 1 and 2 are similar to that of *N*-methyl-*D*-normorphinan, the structure of 3 to those of 6,7-benzomorphan and IV, and the structures of 4 and III to those of I and II. The values for weak analgetic molecules (1–4, III, and IV) are considerably smaller than those for potent ones (I, II, and 6,7-benzomorphan). This structure–activity relationship may support a possible role of ionic association of analgetics with the receptor and the importance of the N–Ph distance for stereochemically controlled binding of analgetics (having an axial relationship between the benzene ring and the nitrogen-containing ring) at the receptor site.[16,17,23]

A priori it would seem reasonable to assume that in vivo transport properties of the homologues of 6,7-benzomorphan should all be quite comparable. A rather speculative but consistent explanation of the N–Ph distance and activity data suggests itself if it is assumed that the cationic nitrogen of homologues of 6,7-benzomorphan interacts with the anionic site of the opiate receptor and the aromatic ring interacts with the lipophilic site to form a drug–receptor complex.[34] The binding affinity could then be greatly affected by the N–Ph distance of the analgetics, and the optimum distance for molecules having a fixed axial conformation of the aromtic ring for the nitrogen-containing ring might be 4.5–4.8 Å.

Experimental Section

All melting points were determined with a micromelting point apparatus (Yanagimoto) and are uncorrected. Microanalyses were performed by the Microanalytical Laboratory, Faculty of Pharmaceutical Sciences, University of Toyama. Where analyses are indicated only by symbols of the elements, the analytical results obtained for these elements were within ±0.4% of the theoretical values. IR spectra were recorded on a Hitachi 215 spectrophotometer. NMR spectra were recorded, at 100 MHz, on a JEOL MH-100 spectrometer with Me_4Si as an internal standard. Mass spectra were recorded on a Hitachi RMU-6MG mass spectrometer.

4-Acetamidomethyl-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (7). A mixture of 6[11] (2.2 g, 11.5 mmol), Ac_2O (10 mL), and AcOH (10 mL) was heated on a water bath for 4 h. After evaporation to dryness, the residual syrup was dissolved in $CHCl_3$, washed with 10% NaOH and 10% HCl, and dried ($MgSO_4$). Evaporation of the solvent gave 2.65 g of yellow syrup, which was dissolved in AcOH (50 mL). To this solution was added a solution of $Na_2Cr_2O_7·2H_2O$ (6.13 g, 20.5 mmol) in 1 N H_2SO_4 (30 mL) with ice cooling and stirring during 10 min, and then 10 N H_2SO_4 (60 mL) was added during 2 h. After stirring was continued at room temperature for 15 h, the mixture was diluted with H_2O, extracted with $CHCl_3$, and dried ($MgSO_4$). Evaporation of the solvent afforded a yellow crystalline mass, which was recrystallized from Me_2CO–Et_2O to give 2.0 g (71%) of 7 as colorless crystals: mp 109.5–110.5 °C; IR (KBr) 3320, 3080 (NH), 1690 (ArC=O), and 1650 cm^{-1} (NHC=O); NMR ($CDCl_3$) δ 1.96 (3 H, s, COMe), 3.77 (3 H, s, OMe), 4.54 (1 H, br s, NH), 4.60–4.76 (2 H, m, C_5- and C_7-H), 7.81 (1 H, d, J = 8.0 Hz, C_8-H). Anal. ($C_{14}H_{17}O_3$) C, H, N.

3-Acetyl-8-methoxy-2,3-dihydro-1,4-methano-1*H*-3-benzazepin-5(4*H*)-one (8). To a stirred solution of 7 (1.3 g, 5.3 mmol) in C_6H_6 (100 mL) and THF (25 mL) was added Br_2 (0.85 g, 5.3 mmol) in THF (10 mL) at room temperature during 30 min. After stirring (1 h) and evaporation to dryness, the residual syrup was mixed with a solution of NaOMe (3.1 g, 57 mmol) in MeOH (30 mL), and the mixture was refluxed for 5 h. After evaporation of the solvent, the residue was treated with $CHCl_3$ and H_2O. The residual syrup from the dried $CHCl_3$ solution was chromatographed on a silica gel (20 g) column. Elution with $CHCl_3$ gave 0.55 g (43%) of 8: mp 121–123 °C (from Me_2CO–Et_2O); IR (KBr) 1695 (ArC=O) and 1640 cm^{-1} (NHC=O); NMR ($CDCl_3$) δ 2.16 (3 H, s, COMe), 3.84 (3 H, s, OMe), 4.38–4.48 (1 H, m, C_4-H), 6.75 (1 H, d, J = 2.0 Hz, C_9-H), 6.83 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_7-H), 7.92 (1 H, d, J = 8.0 Hz, C_6-H); mass spectrum m/e 245 (M^+). Anal. ($C_{14}H_{15}O_3N$) C, H, N.

3-Acetyl-8-methoxy-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (10). To a stirred solution of 8 (2.08 g, 8.2 mmol) in MeOH (70 mL) was added $NaBH_4$ (2.0 g, 5.3 mmol) during 30 min with ice cooling. After stirring was continued at room temperature for 2 h, the solvent was evaporated. The yellow residue was treated with $CHCl_3$ and H_2O. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and evaporated. The solid mass was recrystallized from Me_2CO to give 1.87 g (93%) of 9 as colorless cubes: mp 171–173 °C; IR (KBr) 3440 (NH), 1625 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.86 (3 H, s, COMe), 3.74 (3 H, s, OMe), 4.68–4.88 (1 H, m, C_1-H), 4.93 (1 H, d, J = 3.0 Hz, C_5-H), 6.51 (1 H, d, J = 2.0 Hz, C_9-H), 6.73 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_7-H), 7.38 (1 H, d, J = 8.0 Hz, C_6-H). Anal. ($C_{14}H_{17}O_3N$) C, H, N.

A mixture of the hydroxy derivative 9 (1.87 g, 7.6 mmol), Pd/C (10%, 1.0 g), and $HClO_4$ (70%, 1 mL) in AcOH (30 mL) was shaken in H_2 at 60 °C and atmospheric pressure for 8 h. After removal of the catalyst and the solvent, the crystalline mass was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$, and dried ($MgSO_4$). Evaporation of the solvent gave 1.8 g of crude 10, which was recrystallized from Me_2CO–Et_2O to afford 1.67 g (95.5%) of 10 as colorless crystals: mp 125–127 °C; IR (KBr) 1630 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.87 (3 H, s, COMe), 3.68 (3 H, s, OMe), 6.40–6.90 (3 H, m, aromatic H); mass spectrum m/e 231 (M^+). Anal. ($C_{14}H_{17}O_2N$) C, H, N.

8-Hydroxy-3-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-3-benzazepine (1). A mixture of 10 (1.6 g, 6.9 mmol), 10% NaOH (50 mL), and EtOH (50 mL) was refluxed for 40 h. The mixture was evaporated to dryness, diluted with H_2O, extracted with $CHCl_3$, and dried (K_2CO_3). The residual oil from the $CHCl_3$ solution was distilled in vacuo to give 0.9 g (69%) of a colorless oil: bp 125–135 °C (1 mmHg) (bath temperature); IR (neat) 3350 cm^{-1} (NH). The distillate (0.9 g, 7.8 mmol), HCOOH (15 mL), and HCHO (37%, 10 mL) were heated on a water bath for 1.5 h. The mixture was evaporated, and the residue was dissolved in 5% HCl, washed with C_6H_6, basified with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3). The crude oily residue from the Et_2O solution was distilled to give 0.8 g (83%) of 11: bp 115–125 °C (1 mmHg) (bath temperature). The IR and NMR spectra of this product were superimposable with those of the sample prepared by our previous method:[13] mass spectrum m/e 213 (M^+).

A mixture of 11 (0.8 g, 3.9 mmol) and HBr (47%, 10 mL) was refluxed for 30 min. Evaporation and recrystallization from Me_2CO–MeOH gave 0.65 g (61%) of 1·HBr as colorless plates: mp 227–230 °C. The IR spectrum of this product was superimposable with that of the sample prepared by our previous method.[13] Anal. ($C_{12}H_{15}ON$·HBr) C, H, N.

Methyl 4-Hydroxyimino-6-methoxy-1,2,3,4-tetrahydronaphthoate (13). 4-Oxo-6-methoxy-1,2,3,4-tetrahydronaphthoic acid (**12**)[25] (9.0 g, 41 mmol), 12 M HCl (40 mL), and MeOH (600 mL) were refluxed for 4 h. After evaporation, the residue was dissolved in Et_2O, washed with 5% $NaHCO_3$, and dried ($MgSO_4$). Evaporation and recrystallization from Me_2CO–Et_2O afforded 7.0 g (73%) of the methyl ester of **12**: mp 76–78 °C; IR (KBr) 1695 (ArC=O) and 1745 cm^{-1} (COOMe); mass spectrum m/e 234 (M^+).

A mixture of the keto ester (6.5 g, 28 mmol), NH_2OH·HCl (5 g, 72 mmol), and pyridine (21 mL) in MeOH (120 mL) was refluxed for 3 h. After evaporation, the residue was dissolved in $CHCl_3$, washed with 5% HCl, and dried ($MgSO_4$). The reddish solid mass from the $CHCl_3$ solution was recrystallized from Me_2CO–Et_2O to afford 6.3 g (91%) of **13** as colorless cubes: mp 104–106 °C; IR (KBr) 3250 (OH) and 1725 cm^{-1} (COOMe). Anal. ($C_{13}H_{15}O_4N$) C, H, N.

8-Methoxy-4,5-dihydro-1,4-methano-1*H*-2-benzazepin-3(2*H*)-one (14). Compound **13** (1.2 g, 4.8 mmol) in AcOH (20 mL) and MeOH (20 mL) was shaken with PtO_2 (0.2 g) in a H_2 atmosphere at room temperature for 1.5 h. After removal of the catalyst and solvents, the residual oil was dissolved in 5% HCl, washed with Et_2O, and basified with 10% NaOH. A colorless product which solidified during several hours was filtered and recrystallized from Me_2CO to give 0.68 g (70%) of lactam **14**: mp 210–212 °C; IR (KBr) 3170, 3050 (NH), and 1650 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.77 (3 H, s, OMe), 4.24 (1 H, d, J = 4.0 Hz, C_1-H), 6.62 (1 H, d, J = 2.0 Hz, C_9-H), 6.77 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_7-H), 6.90 (1 H, br s, NH), 7.06 (1 H, d, J = 8.0 Hz, C_6-H); mass spectrum m/e 203 (M^+). Anal. ($C_{12}H_{13}O_2N$) C, H, N.

8-Hydroxy-2-methoxy-2-methyl-2,3,4,5-tetrahydro-1,4-methano-1*H*-2-benzazepine (2). A mixture of **14** (2.1 g, 10 mmol) and $LiAlH_4$ (2.0 g, 53 mmol) in THF (50 mL) was refluxed for 7 h. After cooling, the mixture was treated with H_2O and Rochelle salt solution, extracted with $CHCl_3$, and dried (K_2CO_3). Distillation of the residue from the $CHCl_3$ solution gave 1.8 g (92%) of viscous oil: bp 150–170 °C (2 mmHg) (bath temperature); IR (neat) 3400 cm^{-1} (NH). The distillate (1.8 g, 11 mmol), HCOOH (20 mL), and HCHO (37%, 13 mL) were heated on a water bath for 1.5 h. After evaporation to dryness, the residual oil was dissolved in 5% HCl, washed with C_6H_6, basified with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3) Evaporation of the solvent and distillation of the residual oil gave 1.75 g (90.5%) of **15** as a colorless oil: bp 110–120 °C (0.8 mmHg) (bath temperature); IR (neat) 2780 cm^{-1} (NMe); NMR ($CDCl_3$) δ 2.15 (3 H, s, NMe), 3.66 (1 H, d, J = 4.0 Hz, C_1-H), 3.79 (3 H, s, OMe), 6.56 (1 H, d, J = 2.0 Hz, C_9-H), 6.74 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_7-H), 7.04 (1 H, d, J = 8.0 Hz, C_6-H); mass spectrum m/e 203 (M^+). Compound **15** (1.75 g, 8.6 mmol) and HBr (47%, 10 mL) were refluxed for 0.5 h. After evaporation, the residual syrup was dissolved in H_2O, basified with 15 M NH_4OH, extracted with $CHCl_3$, and dried ($MgSO_4$) The solid mass from the $CHCl_3$ solution was recrystallized from Me_2CO–MeOH to afford 1.5 g (92%) of **2** as colorless sandy crystals: mp 174–177 °C; IR (KBr) 2700–2400 cm^{-1} (OH and N^+H); mass spectrum m/e 189 (M^+) Anal. ($C_{12}H_{15}ON$) C, H, N.

4-Acetamido-6-methoxy-3,4-dihydro-1(2*H*)-naphthalenone (17). 7-Methoxy-1-tetralone (**5**) (10 g, 57 mmol), AcONa (8 g, 98 mmol), NH_2OH·HCl (6.0 g, 86 mmol), EtOH (80 mL), and H_2O (80 mL) were refluxed for 5 h. After evaporation, the mixture was diluted with H_2O, extracted with $CHCl_3$, and dried ($MgSO_4$) The solid mass (11 g) from the $CHCl_3$ solution was hydrogenated over PtO_2 (1.0 g) in MeOH (30 mL) and AcOH (30 mL) After absorption of H_2 had ceased (10 h), the catalyst and solvents were removed, and the resultant oil was dissolved in 5% HCl. The aqueous solution was washed with Et_2O, basified with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3). Evaporation of the solvent gave an amino compound (7.6 g, 76% based on **5**): IR (neat) 3500 and 1610 cm^{-1} (NH_2). The amino compound (3.1 g, 17.5 mmol), AcOH (14 mL), and Ac_2O (14 mL) were heated on 100 °C for 4 h. After evaporation to dryness, the residue was dissolved in $CHCl_3$, washed with 10% NaOH and 10% HCl, and dried ($MgSO_4$). The solid mass **16** (3.6 g) from the $CHCl_3$ solution was mixed with AcOH (280 mL) and $Na_2Cr_2O_7$·$2H_2O$ (7.2 g, 24 mmol) in 1 N H_2SO_4 (180 mL). To this mixture was added 10 N H_2SO_4 (350 mL) dropwise with stirring during 2 h. After stirring for 15 h, the mixture was diluted with H_2O, extracted with $CHCl_3$, and dried ($MgSO_4$). Evaporation and recrystallization from MeOH gave 2.5 g (62%) of **17** as colorless needles: mp 201–203 °C; IR (KBr) 3410, 3080 (NH), 1700 (ArC=O), and 1650 cm^{-1} (NHC=O); mass spectrum m/e 233 (M^+). Anal. ($C_{13}H_{15}O_3N$) C, H, N.

4-Acetamido-6-methoxy-2-carboxymethylene-3,4-dihydro-1(2*H*)-naphthalenone (18). To an ice-cooled mixture of HIO_4·$2H_2O$ (2.3 g, 10 mmol), NaOH (0.39 g, 9.8 mmol), and H_2SO_4 (0.34 g, 3.4 mmol) in H_2O (10 mL) was added a solution of tartaric acid (1.53 g, 10 mmol) in H_2O (2 mL). After stirring at room temperature for 30 min, to this solution were added compound **17** (2.0 g, 8.6 mmol) in EtOH (5 mL) and NaOH (1.62 g, 40 mmol) in H_2O (25 mL) and EtOH (25 mL). The mixture was stirred at room temperature for 15 h and at 60 °C for 10 min, cooled, diluted with H_2O, and washed with Et_2O. Acidification of the aqueous layer with H_2SO_4 yielded a reddish solid mass (2.7 g), which was recrystallized from MeOH to give 2.2 g (88%) of **18** as colorless crystals: mp 235–239 °C; IR (KBr) 3260, 3080 (NH), 3300–2400, 1705 (COOH), 1680 (ArC=O) and 1650 cm^{-1} (NHC=O). Anal. ($C_{15}H_{15}O_5N$) C, H, N.

9-Methoxy-1,2-dihydro-1,5-methano-2-benzazocine-3(4*H*),6(5*H*)-dione (20). Hydrogenation of **18** (6.7 g, 23 mmol) over PtO_2 (0.5 g) in MeOH (100 mL) at room temperature and atmospheric pressure for 5 h gave compound **19** as a colorless oil (5.5 g). A solution of **19** (5.5 g) in 10% HCl (100 mL) and EtOH (100 mL) was refluxed for 20 h and then evaporated to dryness. The residual reddish syrup (4.5 g), EtOH (120 mL), C_6H_6 (65 mL), and 18 M H_2SO_4 (2.3 mL) were refluxed for 8 h. After evaporation, the residual syrup was dissolved in 5% HCl and washed with C_6H_6. Basification of the aqueous solution with NaOH gave 1.3 g (25% based on **18**) of **20** as colorless crystals: mp 245–247 °C (from MeOH); IR (KBr) 3170, 3060 (NH), 1675 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.84 (3 H, s, OMe), 4.30–4.50 (1 H, m, C_1-H), 6.69 (1 H, d, J = 2.0 Hz, C_{10}-H), 6.84 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_8-H), 7.67 (1 H, br s, NH), 7.94 (1 H, d, J = 8.0 Hz, C_7-H); mass spectrum m/e 231 (M^+). Anal. ($C_{13}H_{13}O_3N$) C, H, N.

9-Methoxy-1,2,5,6-tetrahydro-1,5-methano-2-benzazocin-3(4*H*)-one (22). To a stirred solution of **20** (0.7 g, 3 mmol) in MeOH (25 mL) was added $NaBH_4$ (0.7 g, 18.5 mmol) during 0.5 h with ice cooling. After stirring for 2 h at room temperature, the solvent was evaporated. The residue was dissolved in H_2O, extracted with $CHCl_3$, and dried ($MgSO_4$). Evaporation and recrystallization from Me_2CO gave 0.61 g (86%) of **21** as colorless cubes: mp 219–221 °C; IR (KBr) 3300 (OH), 3170 (NH), and 1650 cm^{-1} (C=O). Anal. ($C_{13}H_{15}O_3N$) C, H, N.

A mixture of **21** (0.6 g, 2.6 mmol), Pd/C (40%, 0.2 g), and $HClO_4$ (70%, 1 mL) in AcOH (10 mL) was shaken in H_2 at room temperature and atmospheric pressure for 6 h. After removal of the catalyst and solvent, the residual oil was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$, and dried ($MgSO_4$). Evaporation of the solvent gave 0.57 g of crude **22**, which was recrystallized from Me_2CO–Et_2O to afford 0.53 g (95%) of pure **22** as colorless crystals: mp 162–165 °C; IR (KBr) 3170 (NH) and 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.66 (3 H, s, OMe), 4.18 (1 H, br s, C_1-H), 6.50 (1 H, d, J = 2.0 Hz, C_{10}-H), 6.60 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_8-H), 6.88 (1 H, d, J = 8.0 Hz, C_7-H), 7.52 (1 H, br s, NH); mass spectrum m/e 217 (M^+). Anal. ($C_{13}H_{15}O_2N$) C, H, N.

9-Hydroxy-2-methyl-1,2,3,4,5,6-hexahydro-1,5-methano-2-benzazocine (3). A mixture of **22** (470 mg, 2.2 mmol) and $LiAlH_4$ (0.5 g, 13 mmol) in dioxane (30 mL) was refluxed for 9 h. The mixture was cooled, treated with aqueous Rochelle salt solution, and then extracted with $CHCl_3$. The residue from the dried $CHCl_3$ solution was distilled in vacuo to give 310 mg (71%) of a colorless oil: bp 120–130 °C (1 mmHg) (bath temperature); IR (neat) 3250 cm^{-1} (NH). The distillate (310 mg, 1.5 mmol), HCOOH (3 mL), and HCHO (37%, 2 mL) were heated on a water bath for 1.5 h. After evaporation to dryness, the residual syrup was dissolved in 5% HCl, washed with C_6H_6, made alkaline with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3). Evaporation and distillation in vacuo gave 254 mg (77%) of **23** as a colorless

oil: bp 120–130 °C (1 mmHg) (bath temperature); IR (neat) 2765 cm^{-1} (NMe); NMR ($CDCl_3$) δ 2.12 (3 H, s, NMe), 3.52 (1 H, poorly split t, C_1-H), 3.72 (3 H, s, OMe), 6.41 (1 H, d, J = 2.0 Hz, C_{10}-H), 6.68 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_8-H), 6.96 (1 H, d, J = 8.0 Hz, C_7-H); mass spectrum m/e 217 (M^+).

Compound **23** (253 mg, 1.17 mmol) and HBr (47%, 3 mL) were refluxed for 30 min. Evaporation and recrystallization from Me_2CO–MeOH gave 235 mg (71%) of **3**·HBr as colorless crystals: mp 202–205 °C. Anal. ($C_{13}H_{17}ON$·HBr) C, H, N.

4-(*p*-Methoxybenzyl)cyclohexanone (25). 4-(*p*-Methoxybenzoyl)phenol (**24**) (100 g, 0.4 mol), $NH_2NH_2·H_2O$ (140 mL, 2.8 mol), KOH (140 g, 2.5 mol), and diethylene glycol (900 mL) were heated at 190–200 °C for 16 h. The cooled mixture was diluted with H_2O, acidified with 12 M HCl, and extracted with $CHCl_3$. Drying ($MgSO_4$) and evaporation of the solvent gave 75.5 g of a viscous syrup, which was distilled to give 72 g (77%) of 4-(*p*-methoxybenzyl)phenol as a pale yellow solid mass: bp 165–190 °C (5 mmHg); NMR ($CDCl_3$) δ 3.73 (3 H, s, OMe), 3.82 (2 H, s, $-CH_2-$), 4.60 (1 H, br s, OH), 6.60–7.20 (8 H, m, aromatic H). A mixture of the phenol compound (72 g, 0.34 mol) and NaOEt (1.0 g, 15 mmol) in EtOH (250 mL) was shaken with Raney nickel in an autoclave at 110 kg/cm^2 and 120–140 °C. After removal of the catalyst and solvent, the residual syrup was dissolved in Et_2O, washed with 10% NaOH, and dried (Na_2SO_4). The solvent was evaporated to give 61 g (82.5%) of crude 4-(*p*-methoxybenzyl)cyclohexanol, which was submitted to oxidation without any purification. To a mixture of the cyclohexanol (61 g, 0.28 mol), AcOH (61 mL), and H_2O (91 mL) was added a solution of $Na_2Cr_2O_7·2H_2O$ (33.1 g, 0.11 mol) and 18 M H_2SO_4 (15.5 mL) in H_2O (80 mL) under stirring during 0.5 h. The stirred mixture was warmed at 60 °C for 3 h. After cooling, the mixture was diluted with H_2O, extracted with Et_2O, and washed with 5% $NaHCO_3$. Drying (Na_2SO_4) and evaporation of the solvent yielded 50 g of a viscous syrup, which was distilled to give 46.5 g (77%) of **25** as a pale yellow oil: bp 165–168 °C (3 mmHg); IR (neat) 1730 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.80 (3 H, s, OMe), 6.70–7.27 (4 H, m, aromatic H); mass spectrum m/e 218 (M^+). Anal. ($C_{14}H_{18}O_2$) C, H.

4-Oxo-6-methoxy-1,2,3,4-tetrahydronaphthalene-2-propionic Acid (28). To a suspension of NaH (50% suspension in mineral oil, 10.73 g, 0.22 mol) in EtOH (1 mL) and Et_2O (400 mL) was added a solution of ketone **25** (46.5 g, 0.21 mol) and HCOOEt (25.1 g, 0.34 mol) in Et_2O (130 mL) during 1 h with ice cooling. After stirring at room temperature for 16 h, EtOH (8 mL) was added and stirring continued for another hour. To the mixture was added H_2O (650 mL). The aqueous layer was acidified with 12 M HCl, extracted with Et_2O, and dried ($MgSO_4$). Evaporation of the solvent gave 34 g (65%) of crude **26**, which was used for the next procedure without any purification. A mixture of **26** (34 g, 0.14 mol), 10% NaOH (1100 mL), and H_2O_2 (30%, 550 mL) was stirred at room temperature for 40 h. The mixture was acidified with 12 M HCl, extracted with AcOEt, and dried ($MgSO_4$). After evaporation of the solvent, the residual oily diacid **27** (36 g) was heated with PPA (400 g) at 70 °C for 1 h. Then, the mixture was poured onto ice and extracted with $CHCl_3$. The organic layer was extracted with 10% NaOH, and the aqueous extract was acidified with 12 M HCl, extracted with $CHCl_3$, and dried ($MgSO_4$). Evaporation and recrystallization from EtOH–Et_2O afforded 25 g (73%) of **28** as colorless cubes: mp 134–136 °C; IR (KBr) 3300–2400, 1730 (COOH), and 1700 cm^{-1} (ArC=O). Anal. ($C_{14}H_{16}O_4$) C, H.

Ethyl 6-Methoxy-4-hydroxyimino-1,2,3,4-tetrahydronaphthalene-2-propionate (30). Keto acid **28** (1.0 g, 4 mmol), EtOH (7.4 mL), C_6H_6 (5 mL), and 18 M H_2SO_4 (0.25 mL) were refluxed for 10 h. After evaporation, the residue was dissolved in Et_2O, washed with H_2O and 5% $NaHCO_3$, and dried ($MgSO_4$). Evaporation and distillation in vacuo gave 0.88 g (79%) of **29** as a pale-yellow, solid mass: bp 167–180 °C (4 mmHg); IR (KBr) 1750 (COOEt) and 1700 cm^{-1} (ArC=O); NMR ($CDCl_3$) δ 1.23 (3 H, t, J = 7.0 Hz, OCH_2CH_3), 3.79 (3 H, s, OMe), 4.11 (2 H, q, J = 7.0 Hz, OCH_2CH_3), 7.00–7.19 (2 H, m, C_7- and C_8-H), 7.45 (1 H, d, J = 2.0 Hz, C_5-H); mass spectrum m/e 276 (M^+). A mixture of ester **29** (0.87 g, 3.15 mmol), NH_2OH·HCl (1.12 g, 16 mmol), pyridine (7.9 mL), and EtOH (11.5 mL) was refluxed for 2 h. After evaporation, the residual oil was dissolved in $CHCl_3$, washed with 5% HCl, and dried ($MgSO_4$). Evaporation and recrystallization from AcOEt–Et_2O gave 0.89 g (97%) of **30** as colorless cubes: mp 84–87 °C; IR (KBr) 3300 (OH) and 1750 cm^{-1} (COOEt). Anal. ($C_{16}H_{21}O_4N$) C, H, N.

10-Methoxy-4,5,6,7-tetrahydro-1,6-methano-1*H*-2-benzazonin-3(2*H*)-one (31). A solution of oxime **30** (0.85 g, 2.9 mmol) in AcOH (3 mL) and EtOH (3 mL) was shaken with PtO_2 (0.1 g) in H_2 for 5 h. After removal of the catalyst and solvent, the residue was dissolved in 10% HCl, washed with C_6H_6, basified with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3). The residual oil (0.54 g) from the Et_2O solution was heated at 200 °C (40 mmHg) for 4 h and then distilled at 200–220 °C (bath temperature, 0.15 mmHg). The distillate was dissolved in $CHCl_3$, washed with 5% HCl, and dried ($MgSO_4$). After evaporation of the solvent, the residual solid was recrystallized from Me_2CO–Et_2O to give 217 mg (32% based on **30**) of **31** as colorless prisms: mp 149–152.5 °C; IR (KBr) 3250, 3050 (NH), and 1670 cm^{-1} (C=O); NMR ($CDCl_3$) δ 3.71 (3 H, s, OMe), 4.10–4.35 (1 H, m, C_1-H), 6.70 (1 H, d, J = 2.0 Hz, C_{11}-H), 6.74 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_9-H), 7.00 (1 H, d, J = 8.0 Hz, C_8-H), 7.28 (1 H, br s, NH); mass spectrum m/e 231 (M^+). Anal. ($C_{14}H_{17}O_2N$) C, H, N.

10-Hydroxy-2-methyl-2,3,4,5,6,7-hexahydro-1,6-methano-1*H*-2-benzazonine (4). A mixture of **31** (207 mg, 0.9 mmol) and $LiAlH_4$ (200 mg, 5.3 mmol) in dioxane (20 mL) was refluxed for 8 h. After cooling, the mixture was treated with H_2O and Rochelle salt, extracted with $CHCl_3$, and dried (K_2CO_3). Distillation of the residue from the $CHCl_3$ solution afforded 133 mg (69%) of a colorless oil: bp 140–145 °C (0.8 mmHg) (bath temperature). The distillate (133 mg, 0.61 mmol), HCOOH (1.5 mL), and HCHO (37%, 1 mL) were heated on a water bath for 1.5 h. After evaporation to dryness, the residual oil was dissolved in 5% HCl, washed with C_6H_6, basified with 10% NaOH, extracted with Et_2O, and dried (K_2CO_3). Evaporation and distillation of the resultant oil gave 121 mg (86%) of **32**: bp 125–130 °C (1 mmHg) (bath temperature); IR (neat) 2790 cm^{-1} (NMe); NMR ($CDCl_3$) δ 2.48 (3 H, s, NMe), 3.54 (1 H, d, J = 5.0 Hz, C_1-H), 3.67 (3 H, s, OMe), 6.54 (1 H, d of d, J = 8.0 Hz, J' = 2.0 Hz, C_9-H), 6.75 (1 H, d, J = 2.0 Hz, C_{11}-H), 6.80 (1 H, d, J = 8.0 Hz, C_8-H); mass spectrum m/e 231 (M^+). Compound **32** (121 mg, 0.52 mmol) and HBr (47%, 1.5 mL) were refluxed for 0.5 h. After evaporation to dryness, the residual syrup was dissolved in H_2O, basified with 15 M NH_4OH, extracted with $CHCl_3$, and dried ($MgSO_4$). The viscous syrup from the $CHCl_3$ solution was converted to its hydrochloride and recrystallized from MeOH–Me_2CO to give 111 mg (78%) of **4**·HCl·H_2O: mp 124–127 °C. Anal. ($C_{14}H_{19}ON$·HCl·H_2O) C, H, N.

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Synthesis, Opiate Receptor Affinity, and Conformational Parameters of [4-Tryptophan]enkephalin Analogues[1]

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A series of analogues of the opioid peptide enkephalin with tryptophan substituted for phenylalanine in position 4 was synthesized by the solid-phase method. The [Trp[4]]enkephalin analogues and the corresponding [Phe[4]]enkephalin analogues displayed nearly parallel affinities in the opiate receptor binding assay throughout the series. In a conformational study fluorescence parameters were measured and intramolecular Tyr-Trp distances were estimated on the basis of resonance energy transfer experiments. No gross conformational differences were observed between analogues with widely differing opiate receptor affinity; however, small but significant changes in the intramolecular distance between the phenol ring and the indole moiety and/or in their relative orientation became apparent in some compounds. Identical intramolecular distances of 9.3 ± 0.2 Å between the two aromatic rings were obtained with [Trp[4],Met[5]]enkephalin, [Trp[4],Leu[5]]enkephalin, and the N-terminal tetrapeptide comprised in the latter two analogues, indicating the existence of folded conformations in 2×10^{-5} M aqueous solution and demonstrating conformational analogy between these three peptides. The conformational parameters are discussed in relation to the observed affinities and the putative opiate receptor topography.

Since the recently discovered opioid peptides [Met[5]]-enkephalin (H·Tyr-Gly-Gly-Phe-Met·OH) and [Leu[5]]-enkephalin (H·Tyr-Gly-Gly-Phe-Leu·OH) compete with morphine and its derivatives for opiate binding sites,[2] the enkephalin–opiate receptor system is uniquely suited for studying conformational aspects of a polypeptide–receptor interaction. The multitude of structure–activity relationships established with opiates has provided clues regarding the chemical functions which are critical for binding to the receptor and for activity. On the basis of these studies and taking into account the relatively rigid structure of morphine-derived ligands, descriptions of the opiate receptor topography in terms of binding sites have been put forward.[3-6] It is thus of considerable interest to demonstrate correspondence between critical chemical functions in morphine derivatives and in enkephalin and to establish their relative spatial disposition in the peptide.

In Figure 1 the structural formulas of morphine and a potent derivative of the oripavine family, 7α-[1-(*R*)-hydroxy-1-methyl-3-phenylpropyl]-6,14-*endo*-ethenotetrahydrooripavine (PEO), are compared with that of [Met[5]]enkephalin. Omission[7,8] and acetylation[9,10] of the α-amino group in enkephalin produce an almost complete loss of activity both in the binding assay and in the guinea pig ileum bioassay. Methylation of the α-amino group to the secondary amine corresponding to the situation in normorphine results in an analogue with still good activity and affinity.[11,12] Finally, N-allylation of the tyrosyl residue induces partial antagonist properties[13] in analogy to the strong antagonism observed with *N*-allyl derivatives of morphine (e.g., naloxone). Substitution of phenylalanine for tyrosine leads to a drastic reduction in activity[8] and affinity,[14] which demonstrates the importance of the phenolic hydroxyl group for the interaction with the receptor. This finding is in qualitative agreement with the reduced analgesic activity of nonphenolic benzomorphans compared to the corresponding phenolic compounds.[15] O-Methylation of the tyrosine hydroxyl group engenders a drastic drop in activity[11] as is the case with O-methylated derivatives of morphine (e.g., codeine). Clearly, the ensemble of these results supports the idea of a correspondence between the tyrosine moiety in enkephalin and the phenol ring and tertiary nitrogen in morphine-related compounds. Furthermore, these findings suggest similar

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