Highly Selective κ Opioid Analgesics. 4. Synthesis of Some Conformationally Restricted Naphthalene Derivatives with High Receptor Affinity and Selectivity

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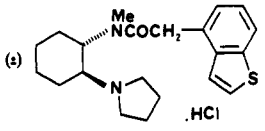
This paper describes the synthesis and κ and μ opioid receptor binding affinity of some conformationally restrained derivatives of the arylacetamide group in the selective κ opioid receptor agonist (±)-*trans*-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-4-acetamide monohydrochloride (1, PD117302), which is an analogue of U-50, 488. The methyl-substituted derivatives (±)-*trans*-*N*,α-dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo-[*b*]thiophene-4-acetamide monohydrochloride (**6a,b**) possess significantly weaker affinity than 1 for the κ opioid receptor (K_i = 172 and 3.7 nM, respectively). It is proposed that this is due to the conformational restriction imposed by the methyl group of **6**. In order to test this proposal the acenaphthene derivative and the 4,5-dihydro-3*H*-naphtho[1,8-*bc*]thiophene derivative were prepared. The acenaphthene derivative (+)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]acenaphthenecarboxamide monohydrochloride (**9**) was found to have high κ opioid receptor affinity and selectivity (κ K_i = 0.37 ± 0.05 nM, μ/κ = 659, δ/κ = 1562) and is 100 times more potent than morphine as an analgesic in the rat paw pressure test for analgesia after intravenous administration (MPE_{50} = 0.014 and 1.4 mg/kg, respectively). The 4,5-dihydro-3*H*-naphtho[1,8-*bc*]thiophene derivative (−)-4,5-dihydro-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3*H*-naphtho[1,8-*bc*]thiophene-5-carboxamide *p*-toluenesulfonate (**17**) also has high κ opioid receptor affinity and selectivity (κ K_i = 4.65 nM, μ/κ = 109).

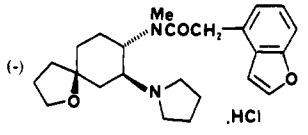
Introduction

Previous studies[1-10] have established that certain *N*-(2-aminocyclohexyl)arylacetamides exhibit high in vitro selectivity and affinity for the κ opioid receptor. These compounds elicit potent analgesia in rodent tests without the undesired μ opioid effects (respiratory depression, dependence-inducing liability, and inhibition of gastrointestinal motility) which characterize morphine and its congeners.[5]

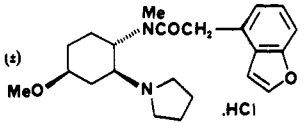
We have previously shown[3,4] that compound 1 (PD 117302) has nanomolar affinity for the κ opioid receptor (K_i = 3.7 nM) and a μ/κ ratio of 110[4] [μ/κ ratio is defined as $K_i(\mu)/K_i(\kappa)$]. The compound is approximately one-half as potent as morphine in the rat paw pressure test for analgesia after oral administration. On the basis of data published by Upjohn,[11] we have synthesized compounds 2 and 3 (PD 129290, CI-977), which have high κ opioid affinity and μ/κ selectivity (κ K_i = 7.1 and 0.83 nM, μ/κ ratio = 465 and 1520, respectively) and significantly more potent analgesic activity than morphine in the rat paw pressure test for analgesia after intravenous administration (MPE_{50} = 0.07, 0.024, and 1.4 mg/kg, respectively).[2] Compound 3 has been selected for further evaluation as an analgesic in clinical trials.



1 (PD 117302)



3 (PD 129290)



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The objective of this study was to synthesize derivatives of the aromatic group of compound 1 in order to further characterize the steric parameters required for high κ receptor affinity and selectivity.

Synthesis

The methodology for the synthesis of the novel amino amides **6**, **8-10** (Schemes I and II, Table I) is the same as that previously described for compounds **1-3**.[2-4] α-Methylbenzo[*b*]thiophene-4-acetic acid (**5**) was prepared by monomethylation of the dianion of benzo[*b*]thiophene-4-acetic acid. A new synthesis of acenaphthene-1-carboxylic acid has been developed[12] while racemic diamine **4**[1] and the optically pure diamine **7**[11] have been prepared as previously described.

Compound **6** is a 1:1 mixture of two diastereoisomers (**6a** and **6b**). One of these diastereoisomers, **6a** or **6b**, was purified from the mixture by medium-pressure chromatography. Compounds **9** and **10** were separated by medium-pressure column chromatography.

The ketone **11** was prepared by the method of Campaigne and Knapp[13] and homologated by treatment with *n*-butyllithium and methyl (methylthio)methyl sulfoxide

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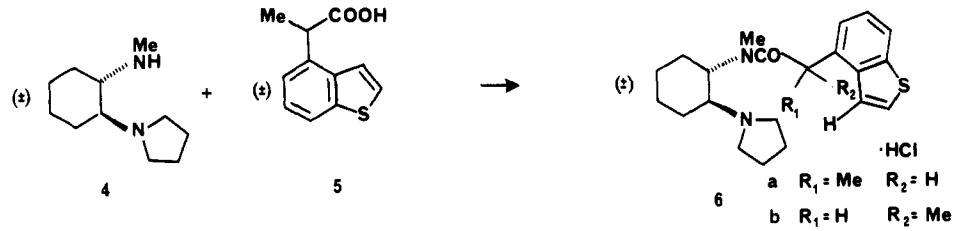
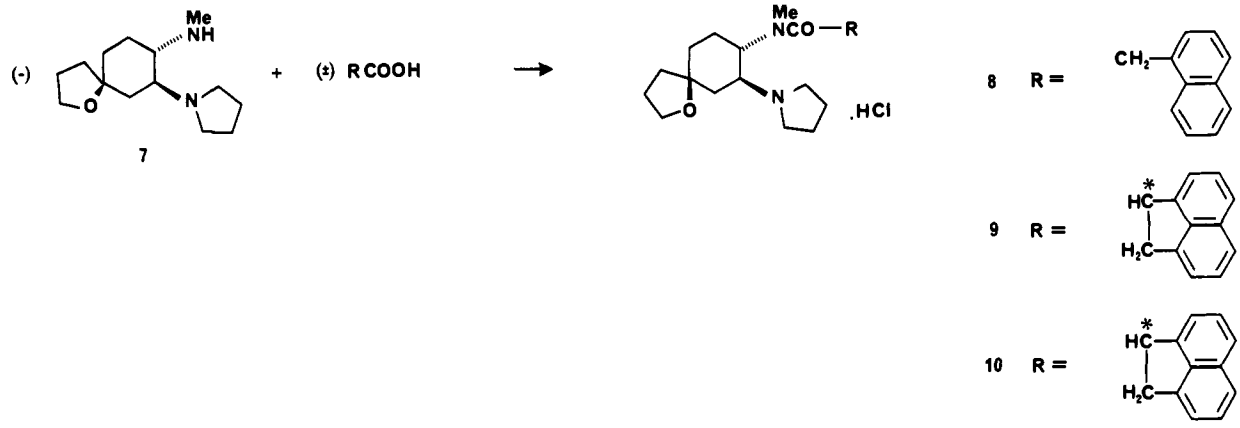
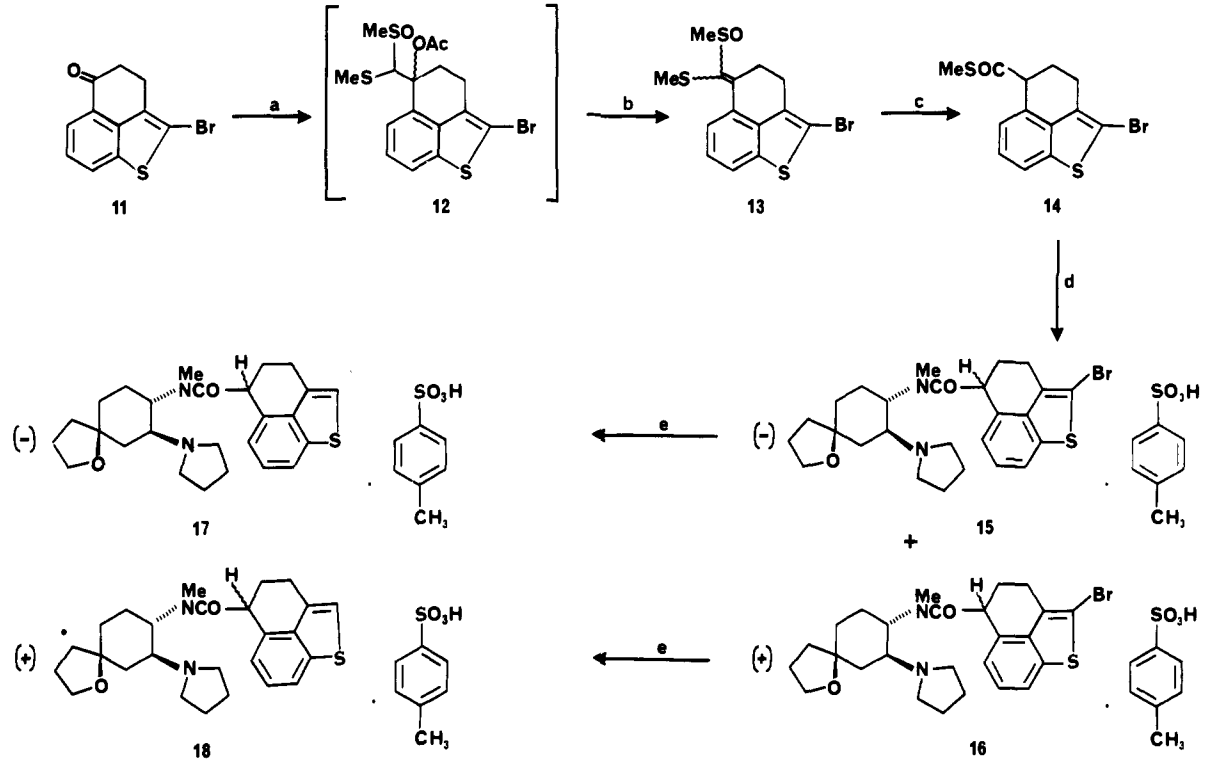
Scheme I



Scheme II



Scheme III[a]



[a] Reagents: (a) (i) *n*-BuLi; $CH_2(SMe)(SOMe)$, (ii) HOAc; (b) KOH; (c) $HClO_4$; (d) (i) amine **7**, $AgOCOCF_3$, (ii) TsOH; (e) (i) *n*-BuLi, (ii) H_2O, (iii) TsOH.

(Scheme III). The intermediate **12** was found to be unstable and was not isolated but converted into the olefin **13**. Treatment with perchloric acid produced the thiol ester **14**, which was coupled with optically pure amine **7** by treating with silver trifluoroacetate. This produced two optically pure diastereoisomers (**15** and **16**), which were separated by chromatography. The absolute stereochemistry of the carbon atom joined to the amide carbonyl is unknown. Removal of the aryl bromide was achieved by lithiation followed by quenching with water, which converted **15** into **17** or **16** into **18**. No racemization was detected, and **17** and **18** were obtained separately, each as a single diastereoisomer.

Results and Discussion

Compound **6** is a 1:1 mixture of two diastereoisomers, **6a** and **6b**, in which either the *pro-R* or the *pro-S* methylene proton of compound **1** is replaced by methyl. The κ opioid receptor affinity of this 1:1 mixture **6** (κ K_i = 172 nM) is 46 times weaker than compound **1** (κ K_i = 3.7 nM).

Table I. Physical Properties of Compounds 6, 8–10, and 13–18

no.	mol formula	mp, °C	anal.	crystn solvent
5	$C_{11}H_{10}O_2S$	119–120	C,H,S	$(CH_3)_2CHOH$–H_2O
6[a]	$C_{22}H_{30}N_2OS\cdot HCl\cdot 0.5H_2O$	229–241	C,H,N	CH_2Cl_2–Et_2O
8	$C_{26}H_{32}N_2O_2CHCl\cdot 0.5H_2O$	189–190	C,H,N	CH_2Cl_2–Et_2O
9	$C_{27}H_{34}N_2O_2\cdot HCl\cdot 0.5H_2O$	143–146	C,H,N	CH_2Cl_2–Et_2O
10	$C_{27}H_{34}N_2O_2\cdot HCl\cdot 1.2H_2O$	138–140	C,H,N	CH_2Cl_2–Et_2O
13	$C_{14}H_{13}BrO_3S$	185–187	C,H,N	$C_6H_5CH_3$
14	$C_{13}H_{11}BrOS_2$	49–51	C,H,N,Br,S	C_6H_{14}
15	$C_{26}H_{33}BrN_2O_2S\cdot C_7H_8O_2S\cdot H_2O$	120–125	C,H,N,Br	$(CH_3)_2CHOH$–Et_2O
16	$C_{26}H_{33}BrN_2O_2S\cdot C_7H_8O_3S\cdot H_2O$	104–108	C,H,N	$(CH_3)_2CHOH$–Et_2O
17	$C_{26}H_{34}N_2O_2S\cdot C_7H_8O_3S\cdot H_2O$	111–114	C,H,N	$(CH_3)_2CHOH$–Et_2O
18	$C_{26}H_{34}N_2O_2S\cdot C_7H_8O_3S\cdot H_2O$	92–95	C,H,N	$(CH_3)_2CHOH$–Et_2O

[a] A 1:1 mixture of two diastereoisomers, 6a and 6b. One of the diastereoisomers was separated and analyzed ($C_{22}H_{30}N_2OS\cdot HCl\cdot 0.5H_2O$) C, H, N.

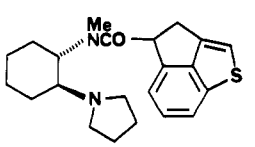
Table II. κ and μ Opioid Binding and Rat Paw Pressure Analgesia Assay

no.	opioid receptor binding affinity: $K_i \pm$ SEM (nM)[a] κ	μ	μ/κ ratio[c]	rat paw pressure assay:[b] iv MPE_{50}, mg/kg
1[d]	3.7 ± 0.4	410 ± 59	11	1.4
3[d]	0.83 ± 0.06	1260 ± 170	1520	0.027
6[e]	172 ± 15	2460 ± 130	14	*f*
8	3.35 ± 0.19	864 ± 135	258	*f*
9[g]	0.37 ± 0.05	244 ± 19	659	0.014
10	1.2 ± 0.1	273 ± 83	227	0.43
15	222 ± 56	3090 ± 870	14	*f*
16	272 ± 78	170 ± 13	0.6	*f*
17	4.65 ± 0.70	507 ± 94	109	*f*
18	11.1 ± 1.4	62 ± 14	5.6	*f*
U-50488H[d]	10 + 1.4	880 ± 44	88	*f*

[a] Each K_i value represents the mean from concentration–response curve performed in triplicate. The μ receptor affinity was determined with ^{3}H-[D-Ala^2-MePhe^4-Glyol^5]enkephalin (DAGOL) and the κ affinity was determined with [^{3}H]etorphine in the presence of excess unlabeled DAGOL and [D-Pen^2,D-Pen^5]enkephalin to suppress μ and δ binding, respectively. [b] MPE_{50} values represent the dose required to produce 50% of the maximum possible analgesic effect. They are derived from a single experiment with six animals at each of five dose levels. [c] μ/κ ratio = $K_i(\mu)/K_i(\kappa)$. [d] Previously reported compound.[1-4] [e] A 1:1 mixture of diastereoisomers 6a and 6b. One of these isomers 6a or 6b was separated and found to have κ K_i = 361 ± 26 nM, μ K_i > 1000. [f] Not tested. [g] δ, opioid receptor affinity was determined to be K_i = 578 ± 25 nM.

One of the diastereoisomers **6a** or **6b** was separated from this mixture and was found to have an affinity for the κ receptor (κ K_i = 361 nM) which is similar to that of the mixture. This indicates that both isomers of **6** have weaker κ opioid receptor affinity than compound **1**.

One explanation for the relative inactivity of the diastereoisomers **6a** and **6b** compared to compound **1** is that the conformation which binds to the κ receptor is one that is less accessible to **6** than to **1**. Two such conformations were identified by examination of Dreiding models.[14] These represent the conformations in which the *C*-methyl group of **6** interacts unfavorably particularly with the proton attached to the C-3 position of the benzo[*b*]-thiophene ring system. This led to the prediction that if a ring is formed between the carbon next to the amide carbonyl of compound **1** and the C-3 position of the aromatic group, then this part of the molecule would be conformationally restricted and it would still possess high affinity for the κ receptor. Based purely on these modelling considerations the first choice was the benzo[*b*]thiophene derivative, compound **19**. However, the synthesis of this



19

[6.5.5] heterocyclic ring system has not been reported in the literature, and due to its anticipated difficulty we decided to prepare the known [6.6.5] acenaphthene ring analogue. We synthesized 1-acenaphthenecarboxylic acid[12] and coupled this to the diamine **7**, which has been shown previously to be optimal for κ receptor activity.[2] This resulted in two diastereoisomers which were separated by chromatography to give compounds **9** and **10**, which have κ K_i = 0.37 and 1.2 nM; μ/κ ratio = 659 and 227, respectively (Table II). Compound **9** was also found to have high selectivity with respect to the δ opioid receptor, δ K_i = 578 nM, δ/κ = 1562. In a rat paw pressure test for analgesia, compound **9** was 100 times more potent than morphine and 31 times more potent than compound **10** after intravenous injection (MPE_{50} = 0.014, 1.4,[4] and 0.43 mg/kg, respectively). For comparison the corresponding conformationally flexible naphthalene analogue **8** was prepared and found to have 9 times weaker affinity for the κ receptor than compound **9** (κ K_i = 3.35 and 0.37 nM, respectively), supporting the hypothesis that the conformational restriction imposed by the acenaphthene system enhances κ receptor affinity.

Encouraged by these results it was decided to investigate the analogous 4,5-dihydro-3*H*-naptho[1,8-*bc*]thiophene derivatives (**17** and **18**). These possess a benzo[*b*]thiophene system conformationally restricted by a six-membered carbocyclic ring. Compound **17** was found to have higher κ opioid receptor affinity and higher μ/κ selectivity than the diastereoisomer **18** or the prototype κ agonist U-50488H (κ K_i = 4.65, 11.1, and 10 nM, respectively, μ/κ ratio = 109, 5.6, and 88, respectively). The difference in activity between **17** and **18** may be due to the different orientation of the aromatic ring with respect to the sub-

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stituents on the cyclohexane.

Conclusion

It is concluded that the aromatic ring of the κ opioid analgesic **3** can be replaced with the acenaphthene ring system or with the 4,5-dihydro-3*H*-naphtho[1,8-*bc*]-thiophene ring system to give compounds **9** and **17**, which have high κ receptor affinity and high μ/κ selectivity.

In compound **9** the orientation of the aromatic ring is conformationally more restrained than it is in compound **8**, and it is proposed that this is an important parameter for binding to the κ opioid receptor.

Experimental Section

Melting points were determined with a Reichart Thermovar hot-stage apparatus and are uncorrected. All NMR spectra were ^{1}H NMR recorded on a Bruker AM 300-MHz spectrometer or a JEOL 60-MHz spectrometer; chemical shifts were recorded in parts per million downfield from tetramethylsilane and coupling constants (*J*) are measured in hertz. IR spectra were recorded with compound (neat) on a sodium chloride disk with a Perkin-Elmer 1750 Fourier transform spectrometer. Optical rotations were determined on a Perkin-Elmer 241 polarimeter. Silica gel used for chromatography was Kieselgel-60 (230–400 mesh) (E. Merck AG, Darmstadt, Germany). Elemental analyses were determined by CHN Analysis Limited, Leicester, U.K. Mass spectra were recorded with a Finnegan 4500 spectrometer.

Benzo[*b*]thiophene-4-acetic acid, 1-naphthylacetic acid, silver trifluoroacetate, and methyl (methylthio)methyl sulfoxide were obtained from the Aldrich Chemical Co. and used without further purification.

α-Methylbenzo[*b*]thiophene-4-acetic Acid (5). *n*-Butyllithium (1.6 M in hexane, 4.0 mL, 6.4 mmol) was added to a solution of benzo[*b*]thiophene-4-acetic acid (0.60 g, 3.1 mmol) in tetrahydrofuran (10 mL) and dimethyl sulfoxide (4 mL) at 0 °C. The resulting solution was stirred at 0–10 °C for 40 min and then methyl iodide (0.19 mL, 3.1 mmol) was added over 4 min and the mixture was allowed to warm to room temperature. After 3 h concentration in vacuo gave an oil which was dissolved in 5% aqueous sodium hydroxide solution (50 mL) and washed with diethyl ether (3 × 30 mL). The aqueous fraction was cooled to 0 °C, acidified with nitric acid, and extracted with dichloromethane (3 × 50 mL). Concentration in vacuo of the dichloromethane fractions followed by silica gel chromatography using ethyl acetate–hexane–acetic acid (70:30:1) as eluant gave a white solid (0.26 g, 1.3 mmol, 42%): NMR ($CDCl_3$, 60 MHz) δ 11.5 (1 H, s, COOH), 7.8–7.2 (5 H, m, Ar-H), 4.15 (1 H, q, *J* = 7), 1.60 (3 H, d, *J* = 7).

(±)-*trans*-*N*,α-Dimethyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzo[*b*]thiophene-4-acetamide Monohydrochloride (6a and 6b). Typical Procedure for Formation of 6 and 8–10. α-Methylbenzo[*b*]thiophene-4-acetic acid (**5**) (98 mg, 0.47 mmol) and 1,1′-carbonylbis-1*H*-imidazole (78 mg, 0.48 mmol) were dissolved in tetrahydrofuran (0.5 mL) and heated to reflux for 30 min. The amine **4**[1] (76 mg, 0.42 mmol) in tetrahydrofuran (0.5 mL) was added and reflux continued for a further 5 h. The mixture was poured into saturated aqueous sodium bicarbonate (30 mL) and extracted with dichloromethane (2 × 20 mL). The dichloromethane layers were concentrated in vacuo to give an oil which was purified by silica gel chromatography using ethyl acetate–hexane–triethylamine (50:50:1) as eluant to give **6a** and **6b** (free base) (1:1 mixture of diastereoisomers) (80 mg, 0.22 mmol, 51%): IR (film) 1638 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.80 (1 H, d, *J* = 8, C_7-H), 7.75 (1 H, d, *J* = 8, C_7-H), 7.67 (1 H, d, *J* = 6, C_2-H), 7.64 (1 H, d, *J* = 6, C_2-H), 7.52 (1 H, d, *J* = 6, C_3-H), 7.47 (1 H, d, *J* = 6, C_3-H), 7.30–7.10 (4 H, m, C_5-H and C_6-H), 4.81 (1 H, q, *J* = 7, C*H*CH_3), 4.39 (1 H, q, *J* = 7, C*H*CH_3), 4.00 (1 H, br s, CHN), 3.92 (1 H, br s CHN), 3.70 (2 H, m, CHN), 3.10 (2 H, m, CHN), 2.90 (3 H, s, NCH_3), 2.73 (3 H, s, NCH_3), 1.56 (3 H, d, *J* = 7, CH_3), 1.54 (3 H, d, *J* = 7, CH_3), 2.7–1.1 (30 H, m). In order to obtain elemental analyses a crystalline hydrochloride salt was prepared by dissolving the above oil (80 mg, 0.22 mmol) in ether (5 mL) and adding an excess of hydrogen chloride in diethyl ether. The white precipitate (64 mg, 0.16 mmol, 73%) was filtered and washed with ether (5 mL).

One of the diastereoisomers was separated from the above mixture of two diastereoisomers by silica gel chromatography using ethyl acetate–hexane–triethylamine (50:50:1) as eluant to give a single diastereoisomer **6a** or **6b** (free base) (40 mg): IR (film) 1637 cm^{-1}; NMR ($CDCl_3$, 300 MH_z) δ 7.80 (1 H, d, *J* = 8, C_7-H), 7.64 (1 H, d, *J* = 6, C_2-H), 7.52 (1 H, d, *J* = 6, C_3-H), 7.30 (1 H, t, *J* = 8, C_6-H), 7.20 (1 H, d, *J* = 8, C_5-H), 4.39 (1 H, q, *J* = 7, C*H*CH_3), 4.0 (2 H, br s, 2 CHN), 3.25 (1 H, br s, CHN), 2.88 (3 H, s, NCH_3), 1.53 (3 H, d, *J* = 7 H, CH_3), 2.9–1.2 (15 H, m). In order to obtain elemental analyses the crystalline hydrochloride derivative was prepared as described above for **6a** and **6b**.

Compounds **9** and **10** were obtained as a mixture of diastereoisomers. This mixture was separated by medium-pressure column chromatography using silica gel (Merck 11695) as stationary phase and dichloromethane–methanol (10:1) as eluant. Compound **9**: $[\alpha]^{20}_D$ = +13.9° (*c* = 0.16, EtOH); MS *m*/*e* (EI$^+$) 419 (100), 207 (20), 166 (15). Compound **10**: $[\alpha]^{20}_D$ = +43.5° (*c* = 0.16, EtOH); MS *m*/*e* (EI$^+$) 419 (100), 207 (21), 166 (14).

2-Bromo-4,5-dihydro-5-[(methylsulfinyl)(methylthio)-methylene]-3*H*-naphtho[1,8-*bc*]thiophene (13). *n*-Butyllithium (1.6 M in hexane, 8.6 mL, 13 mmol) was added to a solution of methyl (methylthio)methyl sulfoxide (1.44 mL, 13.8 mmol) in tetrahydrofuran (70 mL) at 0 °C. The mixture was stirred at 0 °C for 25 min and then cooled to −78 °C and treated with 2-bromo-3,4-dihydro-5*H*-naphtho[1,8-*bc*]thiophen-5-one (**11**) (3.5 g, 13 mmol). After 2 h acetic acid (1.55 mL, 16.4 mmol) was added and the mixture was stirred at 20 °C for 30 min and then poured into saturated aqueous sodium bicarbonate solution (500 mL). This mixture was extracted with dichloromethane (3 × 70 mL) and purified by silica gel chromatography using dichloromethane–methanol (50:1) as eluant to give the acetate **12** as a foam (2.1 g): IR (film) 1734 cm^{-1}. This material was immediately dissolved in dichloromethane (27 mL) and added to a solution of potassium hydroxide (680 mg, 12.1 mmol) in methanol (50 mL) at 5 °C for 1.5 h. The mixture was poured into saturated aqueous sodium bicarbonate (500 mL) and extracted with dichloromethane (3 × 70 mL). Concentration in vacuo of the combined dichloromethane fractions followed by silica gel chromatography using ethyl acetate as eluant gave an off-white solid (3.0 g, 8.0 mmol, 62% from the ketone **11**). An analytically pure sample was obtained by recrystallization from toluene to give yellow needles: IR (film) 3400, 1416 cm^{-1}; MS *m*/*e* (EI$^+$) 375 (10), 373 (9), 358 (17), 356 (16), 311 (41), 309 (41), 296 (49), 294 (50), 107 (100); NMR ($CDCl_3$, 300 MHz) δ 7.73 (1 H, d, *J* = 8, C_7-H), 7.33 (1 H, t, *J* = 8, C_6-H), 7.12 (1 H, d, *J* = 8, C_5-H), 3.6 (1 H, m), 3.2–2.9 (3 H, m), 2.80 (3 H, s, $SOCH_3$), 2.53 (3 H, s, SCH_3).

***S*-Methyl 2-Bromo-4,5-dihydro-3*H*-naphtho[1,8-*bc*]-thiophene-5-carbothioate (14).** The olefin **13** (0.45 g, 1.2 mmol) was dissolved in 1,2-dimethoxyethane (30 mL) containing 70% perchloric acid (4 mL) and stirred in an oil bath at 70–75 °C for 65 min. The resulting solution was basified with saturated aqueous sodium bicarbonate solution (400 mL) and extracted with ether (3 × 50 mL). The combined ether fractions were washed with water (200 mL) and concentrated in vacuo to give a purple oil (0.34 g) which was purified by silica gel chromatography using hexane–ether (15:1) as eluant to give the thioester **14** (162 mg, 0.497 mmol, 41%). An analytically pure sample was obtained by recrystallization from hexane as green needles: IR (film) 1677 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 7.65 (1 H, d, *J* = 8, C_7-H), 7.28 (1 H, t, *J* = 8, C_6-H), 7.22 (1 H, d, *J* = 8, C_5-H), 4.13 (1 H, t, *J* = 5, CHCO), 2.84 (2 H, m), 2.55 (1 H, m), 2.66 (3 H, s, CH_3), 2.10 (1 H, m); MS *m*/*e* (EI$^+$) 328 (14), 326 (13), 253 (62), 251 (65), 171 (100).

2-Bromo-4,5-dihydro-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-3*H*-naphtho[1,8-*bc*]thiophene-5-carboxamide *p*-Toluenesulfonate (15 and 16). The amine **7**[11] (1.0 g, 3.5 mmol) was dissolved in ether (50 mL) and saturated aqueous sodium bicarbonate (50 mL). The ether layer was dried (anhydrous magnesium sulfate) and concentrated in vacuo to give an oil which was dissolved in 1,2-dimethoxyethane (5 mL). This solution was treated with silver trifluoroacetate (0.40 g, 1.8 mmol) and the thiol ester **14** (0.25 g, 0.76 mmol) and stirred at room temperature for 18 h. The mixture was diluted with dichloromethane (200 mL), filtered through Celite, poured into aqueous potassium carbonate (250 mL), and extracted with dichloromethane (200 mL). The dichloromethane fraction was purified

by silica gel chromatography using dichloromethane–methanol (25:1) as eluant to give isomer 1 (206 mg, 0.398 mmol, 52%) and isomer 2 (106 mg, 0.205 mmol, 27%).

Isomer 1 (0.42 g, 0.81 mmol) and *p*-toluenesulfonic acid monohydrate (0.155 g, 0.816 mmol) were dissolved in propan-2-ol (10 mL). The solvent was removed in vacuo and the residue was recrystallized from ether–propan-2-ol (7:1) to give **15** as white needles (0.51 g, 0.74 mmol, 91%): IR (film) 3468 cm^{-1}; NMR δ ($CDCl_3$, 300 MHz) 10.30 (1 H, br s, NH), 7.74 (2 H, apparent (app) d, J = 8, 2 C-H, tosylate), 7.54 (1 H, d, J = 8, C_7-H), 7.28 (1 H, t, J = 8, C_6-H), 7.16 (1 H, d, J = 8, C_5-H), 7.11 (2 H, app d, J = 8, 2 C-H tosylate), 4.65 (1 H, m, CHN), 4.39 (1 H, t, J = 5, CHCON), 4.11 (1 H, m, CHN), 3.85 (2 H, m, CH_2O), 3.65 (1 H, m, CHN), 3.45 (1 H, m, CHN), 3.29 (3 H, s, NCH_3), 3.05 (1 H, m, CHN), 2.93 (1 H, m, CHN), 2.71 (2 H, m, CH_2Ar), 2.33 (3 H, s, Ar-CH_3 tosylate), 1.5–2.2 (16 H, m); MS m/e (EI^+) 519 (91), 517 (90), 448 (74), 446 (74), 325 (100); $[\alpha]^{20}_D$ = −60° (c = 0.78, CH_2Cl_2).

Isomer 2 (0.27 g, 0.52 mmol) and *p*-toluenesulfonic acid monohydrate (99 mg, 0.52 mmol) were dissolved in propan-2-ol (10 mL). The solvent was removed in vacuo and the residue was recrystallized from ether–propan-2-ol (7:1) to give **16** as a white powder (0.32 g, 0.46 mmol, 88%): IR (film) 3467, 1641 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 10.30 (1 H, br s, NH), 7.75 (2 H, app′ d, J = 8, 2 C-H tosylate), 7.54 (1 H, d, J = 8, C_7-H), 7.18 (2 H, app′ d, J = 8, 2 C-H tosylate), 7.16 (1 H, t, J = 8, C_6-H), 6.80 (1 H, d, J = 8, C_5-H), 4.92 (1 H, m, CHN), 4.25 (1 H, m, CHCON), 4.18 (1 H, m, CHN), 3.85 (2 H, m, CH_2O), 3.65 (2 H, m, 2 CHN), 3.29 (3 H, s, NCH_3), 3.15–3.03 (2 H, m, 2 CHN), 2.80 (1 H, m, CHAr), 2.37 (3 H, s, Ar-CH_3 tosylate), 2.5–1.6 (17 H, m); MS m/e (EI^+) 519 (100), 517 (93), 448 (79), 446 (79), 325 (56); $[\alpha]^{20}_D$ = +39° (c = 0.63, CH_2Cl_2).

4,5-Dihydro-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]dec-8-yl]-3*H*-naphtho[1,8-*bc*]thiophene-5-carboxamide *p*-Toluenesulfonate (Isomer 1) (17). The bromo amide **15** (335 mg, 0.486 mmol) was dissolved in tetrahydrofuran (50 mL), cooled to −78 °C, and treated with *n*-butyllithium (1.6 M in hexane, 0.85 mL, 1.4 mmol). After 2 h at −78 °C the mixture was rapidly poured into 1% aqueous sodium carbonate (500 mL) at 25 °C with stirring. The mixture was extracted with dichloromethane (2 × 150 mL), and the organic fractions were concentrated in vacuo and purified by silica gel chromatography using dichloromethane–methanol (25:1) as eluant to give an oil (123 mg, 0.280 mmol). This oil (123 mg, 0.280 mmol) and *p*-toluenesulfonic acid monohydrate (55 mg, 0.29 mmol) were dissolved in propan-2-ol (1 mL) and recrystallized from ether–propan-2-ol (5:1) to give **17** (145 mg, 0.237 mmol, 49% from the bromo amide **15**) as colorless needles: IR (neat) 3401, 1637 cm^{-1}; NMR ($CDCl_3$, 300 MHz) δ 10.20 (1 H, br s, NH), 7.74 (2 H, app′ d, J = 8, 2 C-H tosylate), 7.68 (1 H, d, J = 8, C_7-H), 7.24 (1 H, d, J = 8, C_5-H), 7.18 (1 H, t, J = 8, C_6-H), 7.10 (2 H, app′ d, J = 8, 2 C-H tosylate), 6.95 (1 H, s, C_2-H), 4.62 (1 H, m, CHN), 4.40 (1 H, m, CHCON), 4.15 (1 H, m, CHN), 3.85 (2 H, m, CH_2O), 3.75 (1 H, m, CHN), 3.51 (1 H, m, CHN), 3.29 (3 H, s, NCH_3), 3.10 (1 H, m, CHN), 3.0–2.85 (3 H, m, CHN and CH_2Ar), 2.32 (3 H, s, Ar-CH_3 tosylate), 2.25–1.6 (16 H, m); MS m/e (FAB) 439 (100), 368 (34), 325 (8), 217 (90); $[\alpha]^{20}_D$ = −43° (c = 0.68, CH_2Cl_2).

4,5-Dihydro-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro-[4.5]dec-8-yl]-3*H*-naphtho[1,8-*bc*]thiophene-5-carboxamide *p*-Toluenesulfonate (Isomer 2) (18). The method is the same as described for compound **17** above. The bromo amide **16** (335 mg, 0.486 mmol) was converted into **18** (75 mg, 0.12 mmol, 25% from **16**) as colorless diamonds: IR (neat) 3468, 1642 cm^{-1}; NMR δ ($CDCl_3$, 300 MHz) 10.3 (1 H, br s, NH), 7.75 (2 H, app′ d, J = 8, 2 C-H tosylate), 7.68 (1 H, d, J = 8, C_7-H), 7.18 (1 H, t, J = 8, C_6-H), 7.16 (2 H, app′ d, J = 8, 2 C-H tosylate), 6.96 (1 H, s, C_2-H), 6.79 (1 H, d, J = 8, C_5-H), 4.95 (1 H, m, CHN), 4.35 (1 H, m, CHCON), 4.20 (1 H, m, CHN), 3.88 (2 H, m, CH_2O), 3.78 (1 H, m, CHN), 3.56 (1 H, m, CHN), 3.29 (3 H, s, NCH_3), 3.10 (2 H, m, 2 CHN), 2.95 (1 H, m, CHAr), 2.68 (1 H, m, CHAr), 2.35 (3 H, s, Ar-CH_3 tosylate), 2.4–1.6 (16 H, m); MS m/e (FAB) 439 (10), 368 (3), 325 (9), 217 (100); $[\alpha]^{20}_D$ = +42° (c = 0.37, CH_2Cl_2).

Biological Assay. μ and κ opioid receptor binding assays and analgesia assay were performed as previously described.[3] δ opioid receptor binding assays were performed by the method of Paterson.[15]

Acknowledgment. We thank Dr. I. Pattison for expert technical assistance.

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Common Stereospecificity of Opioid and Dopamine Systems for *N*-Butyrophenone Prodine-like Compounds

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Received April 26, 1990

The two optical isomers of 1-[3-(*p*-fluorobenzoyl)propyl]-3-methyl-4-phenyl-4-propionoxypiperidine (FPP) were obtained by resolution of (±)-*r*-3-methyl-4-phenyl-*c*-4-piperidinol followed by N-alkylation and O-propionylation. These, as well as the racemate, were evaluated for their antinociceptive, opioid, and neuroleptic properties using in vivo and in vitro test systems. The results are remarkable in two respects, namely, the dextrorotatory isomer is consistently the most potent on all tests, and it acts on both opioid (μ) and neuroleptic (D_2) receptors.

In a recent communication, we reported the synthesis of certain 4-phenyl-4-piperidinols, corresponding esters, and related compounds with an *N*-fluorobutyrophenone chain on the nitrogen atom.[1] The synthesis was prompted by the increased interest in compounds with combined analgesic and neuroleptic properties.[2,3] Results of in vivo and in vitro testing revealed that the racemates of two propionoxy derivatives with 3-methyl-4-phenyl relationships like α- and β-prodine, respectively, had potent (μ opioid) analgesic and neuroleptic (D_2) activities.[1] Because the results of biological studies in which racemates are used may be misleading,[4] the optical isomers were prepared for study. Our objective was to ascertain whether the opioid

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0022-2623/91/1834-0194$02.50/0