terial, initial conditions were $[IX] = [IX]_0$ and $[I]_0 = [X]_0 = 0$. Let $[IX] = [IX]_e$ at equilibrium. At intermediate times, $[IX] = [IX]_t$ and $[X]_t = [I]_t = [IX]_0 - [IX]_t$. Measured absorbances are conveniently designated A_0, A_e, and A_t. Equation A1 provides $[IX]_e$ in terms of measured or known quantities, where the ϵ's are appropriate to the wavelength employed and A_{tot} is a calculated hypothetical absorbance corresponding to total conversion of IX into I + X. Equation A2 defines K_{eq}. In order to extract k_f

$$[IX]_e = (A_e - A_{tot})/(\epsilon_{ix} - \epsilon_i - \epsilon_x) \quad (A1)$$

$$K_{eq} = ([IX]_0 - [IX]_e)^2/[IX]_e \quad (A2)$$

from rate data for the preceding equilibration, time-dependent absorbance data and values for $[IX]_0$ and K_{eq} were entered into the computer. The program calculates $[IX]_e$ (eq A2 rearranged) and $[IX]_t$ (eq A3). The slope obtained when the resultant values for $[IX]_t$ are plotted according to eq A4 defines k_f.[37] Treatment of reactions in which IX

$$[IX]_t = [(A_t - A_e)/(A_0 - A_e)]([IX]_0 - [IX]_e) + [IX]_e \quad (A3)$$

$$\ln \frac{[IX]_0^2 - [IX]_e[IX]_t}{[IX]_0([IX]_t - [IX]_e)} = k_f \frac{[IX]_0 + [IX]_e}{[IX]_0 - [IX]_e} t \quad (A4)$$

was generated from equimolar concentrations of I and X ($[IX]_0 = 0$, $[I]_0 = [X]_0$) was similar. Equations A5 and A6 define $[IX]_e$ and K_{eq}, the increase in $[IX]_t$ is proportional to the rise in absorbance from A_0 to A_e, and the slope of a plot of eq A7 plot defines k_b.

$$[IX]_e = (A_e - A_0)/(\epsilon_{ix} - \epsilon_i - \epsilon_x) \quad (A5)$$

$$K_{eq} = ([I]_0 - [IX]_e)^2/[IX]_e \quad (A6)$$

$$\ln \frac{[IX]_e([I]_0^2 - [IX]_t[IX]_e)}{[I]_0^2([IX]_e - [IX]_t)} = k_b \frac{([I]_0^2 - [IX]_e^2)}{[IX]_e} t \quad (A7)$$

(37) Frost, A. A.; Pearson, R. G. *Kinetics and Mechanism*, 2nd Ed.; John Wiley: New York, 1961; pp 186–187.

Synthesis, Opioid Receptor Binding Profile, and Antinociceptive Activity of 1-Azaspiro[4.5]decan-10-yl Amides

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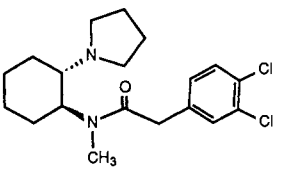
A series of azaspiro[4.5]decanyl amides were prepared by a novel cyclization route and examined for opiate receptor binding and antinociceptive activity. Selected tertiary amides in this series showed potent selective μ-receptor binding and antinociceptive activity, in contrast to the less conformationally restricted secondary amides, which showed relatively weak activity. Although structurally similar to the κ-agonist U-50488H (1), these compounds showed virtually no tendency to bind to the κ-receptor. An X-ray crystal structure of compound (21) confirms that the spirocyclic amine does not cause distortion away from the chair conformation of the cyclohexane ring. Either this receptor has very specific requirements for the orientation of the two nitrogens of these compounds or this ring system fills a portion of space more readily tolerated by the μ- and δ-receptors.

The characterization of multiple opiate receptors[1,2] has given rise to the concept that it may be possible to design novel opiate analgesics lacking the side effects associated with morphine and its congeners. As a result, extensive research has been done to identify new types of compounds and to probe the structural differences between the various opiate receptors.

Research with the selective κ-agonist U50,488 (1)[3] has suggested that such an analgesic will not cause respiratory depression or constipation[4] normally associated with morphine. In addition, this compound appears not to be self-administered,[5] does not cause tolerance to morphine,[6] and may not have as severe withdrawal problems.[7] However, κ-agonists may cause diuresis[8] and undesirable central nervous system (CNS) effects such as dysphoria.



1
U-50,488

An examination of the known cyclohexanediamine analgesics shows that, like the benzomorphans, subtle variations in structure will alter their binding profile.[3,9] It is thought that a key feature of most opiate analgesics is the relative orientation of the aromatic ring to a basic nitrogen. In order to more rigidly define this orientation, we have prepared a series of amino azaspirodecanes to compare with the cyclohexanediamines. The orientation of the basic amine is fixed relative to the cyclohexane ring in this type of structure. Thus only a subset of conformations available to the cyclohexanediamines can be adopted by the azaspirodecanes. This has resulted in the identification of potent analgesics which, while structurally related to 1, do not show affinity for the κ-receptor. In this report, we

(1) Martin, W. R.; Eades, C. G.; Thompson, J. A.; Huppler, R. E.; Gilbert, P. E. *J. Pharmacol. Exp. Ther.* **1976**, *197*, 517.
(2) Gilbert, P. E.; Martin, W. R. *J. Pharmacol. Exp. Ther.* **1976**, *198*, 66.
(3) Szmuszkovicz, J.; VonVoightlander, P. F. *J. Med. Chem.* **1982**, *25*, 1125.
(4) Cowan, A.; Gmerek, D. E. *Trends Pharmacol. Sci.* **1986**, *25*, 1125.
(5) Tang, A. H.; Collins, R. *J. Psychopharm.* **1985**, *85*, 309.
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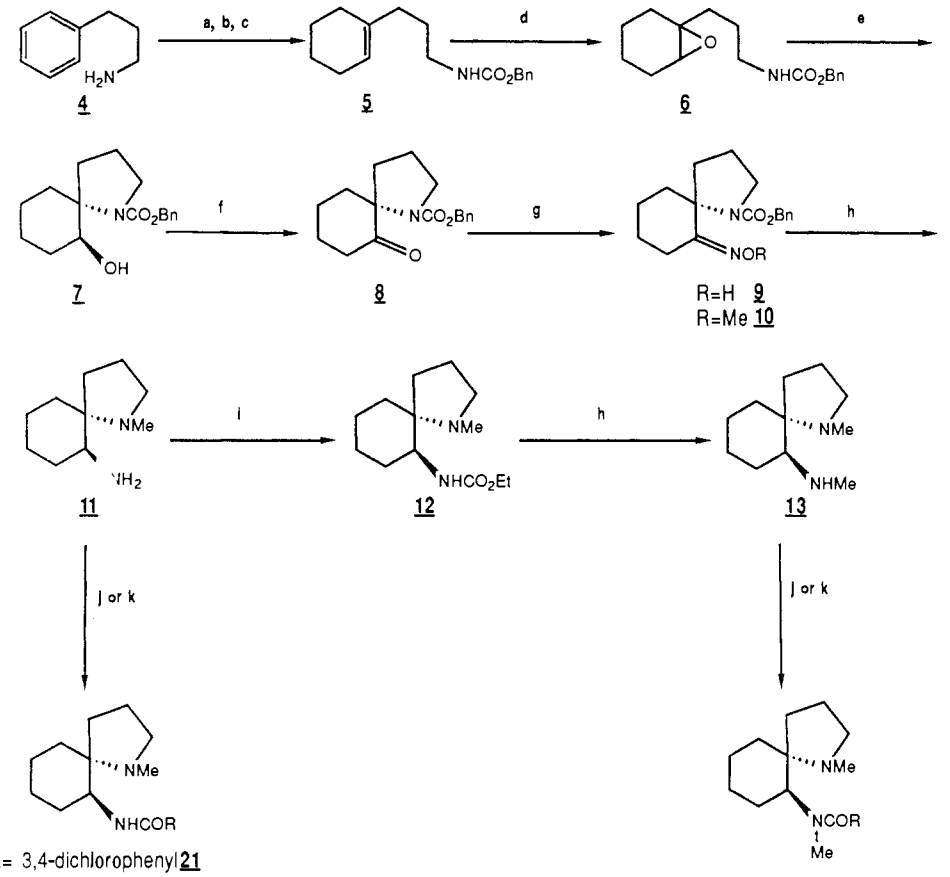
Scheme I[a]

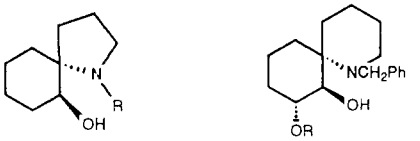


[a] Reagents and conditions: (a) Li, NH_3(l), EtOH; (b) BnOCOCl, Et_3N; (c) H_2, Wilkinson's catalyst; (d) MCPBA; (e) BF_3·Et_2O, −78 °C; (f) PCC; (g) $MeONH_2$·HCl, pyr, or NH_2OH·HCl, pyr; (h) LAH; (i) EtOCOCl, Et_3N; (j) RCOCl, Et_3N; (k) RCOOH, CDI.

outline the synthesis, binding profile, and analgesic activity of these compounds.

Results

Chemistry. A key element in this synthesis is the generation of the 1-azaspiro[4.5]decane (**2**) via an intramolecular epoxide opening. A similar strategy was recently employed in the preparation of the 1-azaspiro[5.5]undecane (**3**).[10] In that case, nucleophilic ring opening of an



2 **3**

amino epoxide was promoted in refluxing toluene. In order to make our synthesis more efficient, we decided to test whether a urethane would be a suitable nucleophile. This would not only serve as a convenient means of protecting the amine, but would also act as a methyl group equivalent.

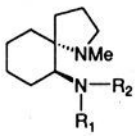
The synthesis of the spirocyclic amino amides is outlined in Scheme I. Birch reduction of the 3-phenylpropylamine (**4**) gave a cyclohexadiene which was acylated with benzyl chloroformate and then reduced with Wilkinson's catalyst to give a 76% overall yield of the cyclohexene **5** after chromatography. Since hydrogenations with heterogeneous catalysts failed to selectively reduce the less substituted olefin, a homogeneous catalyst[11] was employed. Treatment of the cyclohexene **5** with MCPBA gave a 60% yield of the epoxide **6**.

Since the 5-exo mode of cyclization is favored over the 6-endo mode,[12] we expected epoxide opening to give a spiro instead of a fused ring system. In addition, Lewis acid assisted opening of the epoxide should favor cyclization at the more substituted site. Thus treatment of the epoxide **6** with BF_3·Et_2O at −78 °C followed by warming to 0 °C gave a 70% yield of the spirocyclic alcohol **7** as a single stereoisomer.[13] In this case, the urethane, an ambident nucleophile, reacts at nitrogen instead of oxygen. In general, Lewis acids favor attack by oxygen while the use of a strong base favors attack by nitrogen.[14] However, it should be noted that attack by oxygen would lead to the formation of a seven-membered ring.

Since we were unable to replace the alcohol by an amine directly, the alcohol was oxidized to the ketone **8** in quantitative yield with PCC. The oxime **9** and the methoxyoxime **10** were readily prepared from the ketone by stirring it with the appropriate amine in pyridine at room temperature. While LAH reduction of the oxime **9** gave a mixture of diamine stereoisomers, reduction of the methoxyoxime **10** gave a single stereoisomeric diamine (**11**). That the reaction gave a single stereoisomer could be determined by comparing the TLC and ^1H NMR with that of the mixture from reduction of the oxime **9**. In addition, the ^{13}C NMR of the diamine **11** showed a single set of

(10) Tanner, D.; Somfai, P. *Tetrahedron Lett.* **1985**, *26*, 3883.
(11) Hanson, J. C. GB Patent 1315443, 1973.
(12) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734.
(13) Reduction of the ketone **8** with sodium borohydride gave the other isomer whose NMR and TLC properties could be compared with the reaction mixture to show only one isomer was present.
(14) (a) Minami, N.; Ko, S. S.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 1109. (b) Roush, W. R.; Brown, R. J. *J. Org. Chem.* **1982**, *47*, 1371.

Table I. 1-Azaspiro[4.5]decan-10-yl Amides



no.	R_1	R_2	method (% yield)[a]	mp, °C	formula	anal.
14	2-Br-C_6H_4CO	H	A (88)	140–142	$C_{17}H_{23}BrN_2O\cdot HCl$	C, H, N
15	3-Br-C_6H_4CO	H	A (98)	132–133	$C_{17}H_{23}BrN_2O\cdot HCl\cdot H_2O$	C, H, N
16	4-Br-C_6H_4CO	H	A (84)	133–135	$C_{17}H_{23}BrN_2O\cdot HCl$	C, H, N
17	4-Cl-C_6H_4CO	H	A (98)	155–157	$C_{17}H_{23}ClN_2O\cdot HCl\cdot H_2O$	H, N[b]
18	4-F-C_6H_4CO	H	A (89)	118–120	$C_{17}H_{23}FN_2O\cdot C_4H_4O_4$	C, H, N
19	4-MeO-C_6H_4CO	H	A (82)	252–253	$C_{18}H_{26}N_2O_2\cdot HCl$	H, N[c]
20	3,4-di-Cl-C_6H_3CO	H	A (89)	62–63	$C_{17}H_{22}ClN_2O\cdot C_4H_4O_4$	C, H, N
21	3,4-di-Cl-$C_6H_3CH_2CO$	H	B (84)	120–121	$C_{18}H_{24}Cl_2N_2O$	C, H, N
22	4-Br-$C_6H_4CH_2CO$	H	B (97)	110–112	$C_{18}H_{25}BrN_2O\cdot HCl\cdot {}^1/_2H_2O$	C, H, N
23	$C_6H_5CH_2CH_2CO$	H	A (90)	137–139	$C_{19}H_{28}N_2O\cdot C_4H_4O_4\cdot H_2O$	C, H, N
24	4-Br-$C_6H_4SO_2$	H	A (83)	83–85	$C_{16}H_{23}BrN_2O_2S\cdot C_2H_2O_4$	C, H, N
25	4-BrC_6H_4CO	CH_3	A (91)	228–230	$C_{18}H_{25}BrN_2O\cdot HCl$	C, H, N
26	4-CH_3-C_6H_4CO	CH_3	A (93)	174–175	$C_{19}H_{28}N_2O\cdot C_4H_4O_4$	C, H, N
27	4-CF_3-C_6H_4CO	CH_3	A (98)	223–225	$C_{19}H_{25}F_3N_2O\cdot HCl$	C, H, N
28	3,4-di-Br-C_6H_3CO	CH_3	A (81)	83–85	$C_{18}H_{24}Br_2N_2O\cdot C_4H_4O_4$	C, H, N
29	3,4-di-Cl-C_6H_3CO	CH_3	A (80)	145–147	$C_{18}H_{24}Cl_2N_2O\cdot C_4H_4O_4$	C, H, N
30	3,4-di-Cl-$C_6H_3CH_2CO$	CH_3	B (87)	173–175	$C_{19}H_{26}Cl_2N_2O\cdot HCl\cdot H_2O$	C, H, N
31	2-Cl, 4-Br-C_6H_3CO	CH_3	A (76)	148–150	$C_{18}H_{24}BrClN_2O\cdot HCl$	C, H, N
32	2-CH_3, 4-Br-C_6H_3CO	CH_3	A (66)	117–119	$C_{19}H_{27}BrN_2O\cdot H_2O$	H, N[d]
33	4-Br-C_6H_4CO	$CpCH_2$[e]	A (86)	155–156	$C_{21}H_{29}BrN_2O\cdot C_4H_4O_4$	C, H, N
34	4-Br-C_6H_4CO	*i*-Bu	A (71)	125–127	$C_{21}H_{31}BrN_2O$	C, H, N

[a] Yields of the free base are reported. [b] C: calcd, 63.79; found, 63.18. [c] C: calcd, 52.66; found, 52.21. [d] C: calcd, 53.84; found, 54.33. [e] Cp = cyclopropyl.

resonances. Since the stereochemistry could not be assigned unequivocally by NMR, the diamine was converted to the 3,4-dichlorophenylacetamide **21**. The X-ray crystal structure of this compound showed that LAH reduction had given the desired *trans*-diamine. Undoubtedly, the bulky benzyl carbamate prefers to be situated equatorial to the cyclohexane ring. Axial attack by LAH would give the observed stereochemical outcome of this reaction. Acylation of the diamine **11** gave a series of amides (Table I) which were examined for opiate binding activity.

The *N*-methyl amides were prepared from the diamine **11** by acylating the primary amine with ethyl chloroformate to give the urethane **12**, which was then reduced with LAH to give a 76% overall yield of the diamine **13**. Acylation of this diamine gave a series of *N*-methyl amides which were tested for opiate binding activity.

X-ray Crystal Structure Determination. As described above, the relative stereochemistry of the two nitrogen atoms were assigned on the basis of the X-ray structure of the amide **21**. This compound crystallizes with two crystallographically nonequivalent molecules A and B. These two molecules cannot be interconverted by using a symmetry element or by translation. Figure 1 shows the atom numbering and the bond lengths. Within the tolerance limits, no difference could be determined between the bond lengths of the two molecules.

Figure 2 shows the torsion angles. As can be seen in the figure, molecules A and B are in different conformations. The arrangement of the substituents around the pyrrolidine nitrogen atom in both molecules is pyramidal. The distance between N-1 and the plane formed by its substituents C-2, C-3, and C-6 is 0.38 Å. The distance between N-24 and the plane formed by its substituents C-25, C-26, and C-29 is 0.42 Å.

As can be seen in Figure 2, the cyclohexane ring in molecule B exists in a virtually undistorted chair conformation, as the dihedral angles are nearly 60°. The pyrrolidine ring exists in a conformation having C-29, C-28, C-27, and C-26 nearly coplanar and N-24 puckered out of

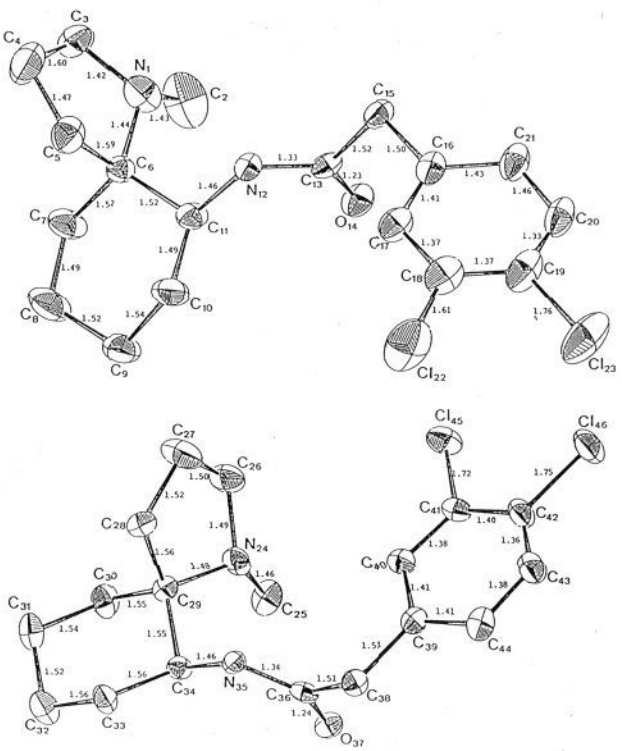
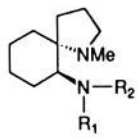


Figure 1. Atom numbering and bond lengths.

the plane formed by the carbons. The hydrogen on the amide nitrogen, N-35, is pointed toward C-28 of the pyrrolidine ring.

This contrasts with molecule A, where the hydrogen on N-12 is pointed toward C-5 of the pyrrolidine ring. The carbon atoms of this ring are slightly distorted so they are no longer coplanar. A slight flattening of the cyclohexane ring is evidenced by the smaller dihedral angles of this molecule. In either case, the plane formed by the three

Table II. Receptor Binding and Antinociceptive Activity of 1-Azaspiro[4.5]decan-10-yl Amides



no.	R_1	R_2	μ^a (nM)	κ^a (nM)	δ^a (nM)	writhing (sc):[b] ED_{50}, mg/kg	tail flick (sc):[b] ED_{50}, mg/kg
14	2-Br-C_6H_4CO	H	>10000	>10000	>10000		
15	3-Br-C_6H_4CO	H	>10000	>10000	>10000		
16	4-Br-C_6H_4CO	H	600 (10)	>10000	>10000	3.28 (1.41–6.35)	inactive
17	4-Cl-C_6H_4CO	H	550 (9)	>10000	>10000		
18	4-F-C_6H_4CO	H	>10000	>10000	>10000		
19	4-MeO-C_6H_4CO	H	2200 (48)	>10000	>10000		
20	3,4-di-Cl-C_6H_3CO	H	210 (7)	>10000	>10000	7.14 (5.12–10.87)	inactive
21	3,4-di-Cl-$C_6H_3CH_2CO$	H	250 (10)	5800 (290)	>10000	inactive	inactive
22	4-Br-$C_6H_4CH_2CO$	H	720 (14)	>10000	>10000		
23	$C_6H_5CH_2CH_2CO$	H	>10000	>10000	2800 (48)		
24	4-Br-$C_6H_4SO_2$	H	>10000	>10000	>10000		
25	4-Br-C_6H_4CO	CH_3	17 (1)	>10000	670 (23)	0.05 (0.02–0.1)	0.17 (0.03–0.36)
26	4-CH_3-C_6H_4CO	CH_3	150 (3)	>10000	>10000		6.39 (3.92–20.48)
27	4-CF_3-C_6H_4CO	CH_3	12 (1)	>10000	670 (45)		
28	3,4-di-Br-C_6H_3CO	CH_3	2 (0.05)	2300 (190)	105 (10)	0.02 (0.007–0.07)	0.21 (0.098–0.36)
29	3,4-di-Cl-C_6H_3CO	CH_3	6.3 (0.05)	>10000	309 (20)	0.045 (0.026–0.079)	0.18 (0.098–0.36)
30	3,4-di-Cl-$C_6H_3CH_2CO$	CH_3	87 (1)	>10000	>10000		
31	2-Cl, 4-Br-C_6H_3CO	CH_3	16 (1.0)	9000 (480)	>10000		
32	2-CH_3, 4-Br-C_6H_3CO	CH_3	21 (1)	>10000	880 (48)		8.72 (7.05–11.24)
33	4-Br-C_6H_4CO	$CpCH_2$[c]	220 (6)	6300 (810)	2800 (140)		
34	4-Br-C_6H_4CO	*i*-Bu	580 (11)	>10000	>10000		

[a] IC_{50} determined, $N = 3$; standard deviation in parentheses. Standards used were levorphanol IC_{50} (μ) = 0.6 ± 0.03 nM; IC_{50} (δ) = 2.9 ± 0.1 nM; and ethylketocyclazocine IC_{50} (κ) = 12 ± 1 nM. [b] 95% confidence limits in parentheses; inactive means less than 50% of the animals were protected at a dose of 30 mg/kg. [c] Cp = cyclopropyl.

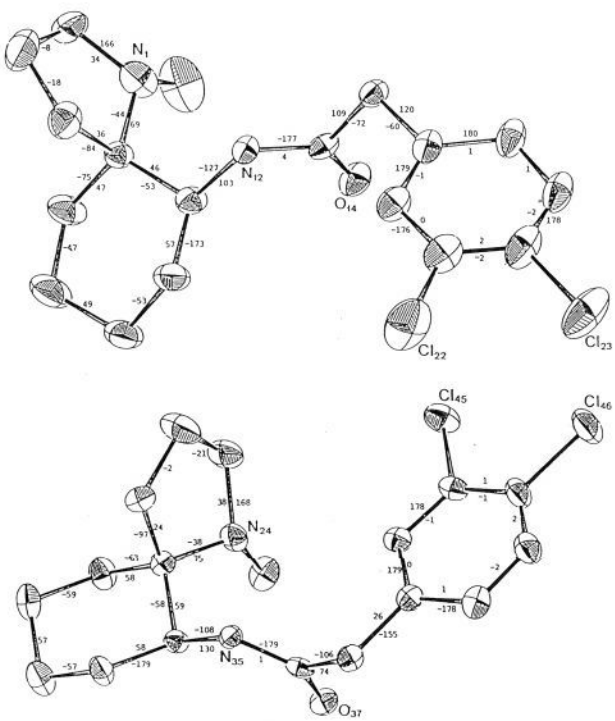


Figure 2. Torsion angles.

carbons adjacent to the pyrrolidine nitrogen is nearly perpendicular to the cyclohexane ring.

Biological Results and Discussion. The spirocyclic amides were tested in standard binding assays for μ-, κ-, and δ-receptors as described in the Experimental Section. Table II lists the IC_{50} values for these compounds. Selected compounds were then tested for in vivo analgesia in the mouse phenylquinone writhing and tail-flick assays. The analgesic activities listed in Table II were measured 30 min after subcutaneous administration of the compound.

The only secondary amides which showed activity in the binding assay contained a 4-bromo (**16**), 4-chlorobenzamide (**17**), or 3,4-dichlorobenzamide (**20**). Affinity for the μ-receptor was enhanced by a factor of 2.5 with an additional halogen in the 3,4-dichlorobenzamide (**20**). The 2-bromo- and 3-bromobenzamides **14** and **15** were inactive at all three receptors. Compounds **16** and **20**, which had only moderate activity at the μ-receptor, had weak activity in the writhing assay and were inactive in the mouse tail-flick assay. The phenylpropionamide **23**, although not very potent, was the only compound to have a ratio for $\delta/\mu < 1$. None of the secondary amides showed appreciable binding at the κ-receptor.

In contrast to the secondary amides, the more conformationally restricted tertiary *N*-methyl amides showed markedly increased μ and δ binding, as well as potent activity in the writhing and tail flick assays. Again, para substitution on the aromatic amide was important for activity. For example, the *N*-methyl-4-bromobenzamide **25** was nearly 35 times more active in μ binding than the corresponding secondary amide **16**. The 2,4-disubstituted amides **31** and **32** showed no improvement over the 4-bromobenzamide **25** in binding. However, the 2-methyl-4-bromobenzamide **32** was 50-fold less potent than the 4-bromobenzamide **25** in the tail-flick assay. Like the secondary amide **20**, the 3,4-dihalobenzamides **28** and **29** had even better μ binding than the monohalo compound **25**. These compounds showed no further improvement in in vivo activity. Moderate affinity in δ binding was seen for this series, with a δ/μ ratio of about 50. The amides **21**, **28**, **31**, and **33** were the only compounds in this series to show κ binding (5800, 2300, 9000, and 6300 nM, respectively).

It is interesting to note that despite its structural similarity to **1**, the 3,4-dichlorophenylacetamide **30** does not bind to the κ-receptor. There are two methylene groups

in the pyrrolidine ring of compound **30** which occupy a portion of space that cannot be filled by any pyrrolidine rotamer of **1**. Either the κ-receptor cannot tolerate the added bulk of these methylene groups or it requires having the amine lone pair (and thus the aromatic amide) in a different orientation relative to the cyclohexane template.

By limiting the possible orientations which can be assumed by the basic nitrogen, we have generated a series of compounds which show high selectivity for the μ-receptor over the κ- and δ-receptor. Selectivity for the κ-receptor could not be achieved by adding spacer groups between the amide and the aromatic ring as had been done with the cyclohexanediamine series.[3,9]

Experimental Section

Melting points were determined on a Thomas-Hoover Uni-Melt apparatus and were not corrected. ^{1}H NMR spectra were recorded on a Perkin-Elmer R12 or R600 spectrometer with tetramethylsilane as internal standard. All intermediates gave NMR spectra which were consistent with the assigned structures. ^{13}C NMR were recorded on a Varian XL-400 spectrometer. IR spectra were recorded on a Perkin-Elmer 281B spectrophotometer, and mass spectra were taken on a Hewlett-Packard HP-5985 mass spectrometer.

1,4-Cyclohexadiene-1-propanamine (35). A solution of 25 g (0.185 mol) of 3-phenyl-1-propylamine in 60 mL of absolute ethanol was added dropwise to 1.2 L of liquid ammonia at −78 °C. The resultant solution was warmed to reflux, and lithium wire was added until the blue color persisted. After the dropwise addition of 25 mL of absolute ethanol, more lithium was added until the color persisted. After the mixture was stirred for 30 min, 40 g of NH_4Cl was added and the ammonia was allowed to evaporate overnight. The residue was dissolved in 1 L of water and extracted three times with CH_2Cl_2. The combined organic layers were washed with water and saturated brine and then dried (Na_2SO_4). The solvent was removed in vacuo to give 22.3 g of an oil that was used without purification: ^{1}H NMR ($CDCl_3$) δ 5.8 (m, 2 H), 5.5 (m, 1 H), 2.1 (t, 2 H, J = 7 Hz).

Benzyl *N*-[3-(1,4-Cyclohexadien-1-yl)propyl]carbamate (36). A solution of benzyl chloroformate (42 mL, 0.3 mol) in 250 mL of CH_2Cl_2 was added over 3 h to a solution of amine **35** (26.8 g, 0.2 mol) in 50 mL of pyridine at −10 °C. The solution was warmed to room temperature and stirred for 18 h. After cooling of the solution to 0 °C, 125 mL of 4:1 CH_3CN/H_2O was added. The organic layer was washed with water, 6 N HCl (three times), and saturated brine. After drying (Na_2SO_4), the solvents were evaporated in vacuo to give 62 g of an oil which was used without purification: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.7 (br, 2 H), 5.4 (m, 1 H), 5.1 (s, 1 H), 5.0 (s, 2 H), 3.1 (q, 2 H, J = 7 Hz).

Benzyl *N*-[3-(1-Cyclohexenyl)propyl]carbamate (5). A solution of the urethane **36** (25 g, 0.092 mol) and tris(triphenylphosphine)rhodium(I) chloride (2 g, 2.2 mmol) in 250 mL of THF (degassed) was hydrogenated at 1 atm pressure for 24 h. The solvent was evaporated in vacuo and the residue was purified by flash chromatography (15% EtOAc/hexane) to give 19 g (76%) of the urethane **5** as an oil: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.4 (m, 1 H), 5.1 (s, 2 H), 3.1 (q, 2 H, J = 6 Hz); MS m/z 273 (M^+).

Benzyl *N*-(3-Oxabicyclo[4.1.0]heptan-1-ylpropyl)carbamate (6). To a solution of 11 g (0.04 mol) of the urethane **5** in 110 mL of CH_2Cl_2 at 0 °C was added 14 g (0.08 mol) of *m*-chloroperbenzoic acid in portions. The resultant suspension was warmed to room temperature and stirred for 18 h. The solid was filtered and washed with CH_2Cl_2. The solution was diluted with 300 mL of ether and washed three times with 2 N NaOH. The combined aqueous layers were extracted with ether. The combined organic layers were washed with saturated brine and dried (Na_2SO_4), and the solvents were evaporated in vacuo. The oil was purified by flash chromatography (50% ether/hexane) to give 7 g (60%) of the epoxide **6** as a solid: ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.1 (s, 2 H), 3.2 (m, 2 H), 2.9 (m, 1 H); MS m/z 289 (M^+).

Benzyl 10-Hydroxy-1-azaspiro[4.5]decane-1-carboxylate (7). To a solution of 2 g (6.92 mmol) of the epoxide **6** in 50 mL of CH_2Cl_2 at −78 °C was added 1.1 mL (9.00 mmol) of BF_3·Et_2O. The reaction was stirred for 3.5 h, warmed to 0 °C, and quenched with saturated $NaHCO_3$. The mixture was extracted three times with CH_2Cl_2, the organic layers were dried (Na_2SO_4), and the solvents were evaporated in vacuo to give 1.4 g (70%) of the alcohol **7** as a solid: IR (CH_2Cl_2) 3590, 3440, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.1 (s, 2 H), 3.5 (m, 2 H); MS m/z 290 (M^+ + 1).

Benzyl 10-Oxo-1-azaspiro[4.5]decane-1-carboxylate (8). To a suspension of 7.0 g (33 mmol) of pyridinium chlorochromate in 600 mL of CH_2Cl_2 was added 3.5 g (12 mmol) of the alcohol **7**. After the mixture was stirred for 18 h, Celite was added, and the mixture was filtered. The solution was washed twice with saturated $NaHCO_3$. The aqueous layers were extracted with CH_2Cl_2. The combined organic layers were dried (Na_2SO_4) and the solvents evaporated in vacuo. Purification by flash chromatography (60% ether/hexane) gave 3.5 g (100%) of the ketone **8** as a colorless oil: IR (CH_2Cl_2) 1720, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.1 (s, 1 H), 3.6 (d, 1 H, J = 6 Hz); MS m/z 287 (M^+).

Benzyl 10-(Methoxyimino)-1-azaspiro[4.5]-decane-1-carboxylate (10). Methoxyamine hydrochloride (4.5 g, 54 mmol) was added to a solution of 2.5 g (8.7 mmol) of the ketone **8** in 5 mL of pyridine and the mixture was stirred for 18 h. Water was added and the mixture was basified with 4 N NaOH. The mixture was extracted three times with CH_2Cl_2, the organic layers were dried (Na_2SO_4), and the solvents were evaporated in vacuo to give 2.45 g (89%) of an oil: IR (CH_2Cl_2) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 5.1 (m, 2 H), 3.7 (s, 3 H); MS m/z 316 (M^+).

1-Methyl-1-azaspiro[4.5]decan-10-amine (11). A THF (30 mL) solution of 2.1 g (6.7 mmol) of the oxime **10** was added dropwise to 2.6 g (6.7 mmol) of LAH in 30 mL of THF at 0 °C. The mixture was warmed to room temperature and stirred for 5 h. The reaction was cooled to 0 °C and quenched by adding dropwise 2.6 mL of water followed by 2.6 mL of 15% NaOH followed by 7.8 mL of water. The mixture was stirred for 1 h, and the salts were filtered and washed with ether. The solvents were evaporated in vacuo, and the residue was dissolved in ether. The ether was extracted three times with 2 N HCl. The aqueous layer was washed with ether, basified with 4 N NaOH, and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), and the solvents were evaporated in vacuo to give 1.3 g of the diamine **11**: ^{1}H NMR ($CDCl_3$) δ 2.2 (s, 3 H); ^{13}C NMR ($CDCl_3$) 22.6, 23.2, 25.0, 28.0 (2 C), 32.5, 33.2, 52.4, 53.7, 65.6; MS m/z 168 (M^+).

Ethyl *N*-(1-Methyl-1-azaspiro[4.5]decan-10-yl)carbamate (12). A solution of 4.3 mL (45 mmol) of ethyl chloroformate in 20 mL of CH_2Cl_2 was added dropwise to a solution of 2.5 g (15 mmol) of the diamine **11** and 6.2 mL (45 mmol) of Et_3N in 20 mL of CH_2Cl_2 at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. Cold water was added and the mixture was stirred for 1 h. The layers were separated, and the organic layer was washed with dilute NaOH solution and brine. The solution was dried (Na_2SO_4), and the solvents were evaporated in vacuo to give 3.5 g (97%) of a yellow oil which was used without purification: ^{1}H NMR ($CDCl_3$) δ 4.1 (q, 2 H, J = 8 Hz), 2.2 (s, 3 H), 1.2 (t, 3 H, J = 8 Hz); MS m/z 240 (M^+).

***N*,1-Dimethyl-1-azaspiro[4.5]decan-10-amine (13).** To a suspension of 2.3 g (60 mmol) of LAH in 30 mL of THF at 0 °C was added a solution of 3.5 g (15 mmol) of the diamine **13** in 40 mL of THF. The mixture was allowed to warm to room temperature and stirred 1.5 h. The reaction was cooled to 0 °C and quenched by adding 2.3 mL of water, 3 mL of 15% NaOH, and then 6.9 mL of water. The salts were filtered and washed with ether, the organic layer was dried (Na_2SO_4), and the solvents were removed in vacuo. Vacuum distillation gave 2.1 g (78%) of the diamine **14** as a colorless oil: ^{1}H NMR ($CDCl_3$) 2.4 (s, 3 H), 2.2 (s, 3 H); MS m/z 182 (M^+).

Benzyl 10-(Hydroxyimino)-1-azaspiro[4.5]decane-1-carboxylate (9). A solution of 205 mg (0.71 mmol) of the ketone **8** and 100 mg (2.8 mmol) of hydroxylamine hydrochloride in 1 mL of pyridine was stirred for 20 h. The pyridine was removed in vacuo and the residue was taken up in water and acidified to pH 1 with 2 N HCl. The mixture was extracted three times with ether, the combined organic layers were dried ($Na_2SO_4/MgSO_4$), and the solvents were evaporated in vacuo to give 219 mg (100%) of a white solid which was used without purification: IR (CH_2Cl_2) 1700 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.1 (br, 1 H), 7.3 (m, 5 H), 5.1 (s, 2 H); MS m/z 302 (M^+).

1-Methyl-1-azaspiro[4.5]decan-10-amine (11). A solution of 30 mg (0.099 mmol) of the oxime **9** in 1 mL of THF was added dropwise to 0.7 mmol of LAH in 1.7 mL of THF at 60 °C. The reaction was stirred for 5 min, cooled to 0 °C, and quenched with saturated sodium potassium tartrate. The salts were filtered and washed with CH_2Cl_2. Water and a few drops of 2 N NaOH were added, the layers were separated, and the aqueous layer was extracted twice more with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), and the solvents were evaporated in vacuo to give 21 mg of a mixture of diastereomeric diamines as an oil: ^1H NMR ($CDCl_3$) δ 2.3 (s, 3 H), 2.2 (s, 3 H).

Preparation of *N*-(1-Methyl-1-azaspiro[4.5]decan-10-yl) Amides. Method A. To a solution of 119 mg (0.7 mmol) of the diamine **11** and 0.3 mL of triethylamine (2.2 mmol) in 5 mL of CH_2Cl_2 was added 156 mg (0.7 mol) of 4-bromobenzoyl chloride. After the mixture was stirred for 1 h, water and 2 mL of 2 N NaOH were added, and the mixture was stirred for 1 h. The layers were separated, and the aqueous layer was extracted with CH_2Cl_2. The organic layers were dried (Na_2SO_4) and the solvents evaporated in vacuo to give 150 mg of a yellow powder. The free base was converted to the HCl salt with HCl/ether. Recrystallization from ethyl acetate gave 100 mg (37%) of the amide **16**: mp 133–135 °C; IR (KBr) 3420, 3220, 1660 cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.1 (m, 2 H), 7.6 (m, 2 H), 2.8 (m, 2 H), 2.8 (s, 3 H). Anal. ($C_{17}H_{23}BrN_2O$·HCl) C, H, N.

Method B. A solution of 294 mg (1.8 mmol) of 1,1′-carbonyldiimidazole and 369 mg (1.8 mmol) of 3,4-dichlorphenylacetic acid in 10 mL of CH_2Cl_2 was stirred for 2 h. A solution of 200 mg (1.18 mmol) of the diamine **11** in 10 mL of CH_2Cl_2 was added and the mixture was stirred an additional 2 h. The reaction was quenched with 20 mL of 2 N NaOH, and the layers were separated. The aqueous layer was extracted twice with CH_2Cl_2, the combined organic layers were dried (Na_2SO_4), and the solvents were evaporated in vacuo to give 355 mg of the amide **21** as a yellow powder. Flash chromatography (5% saturated NH_3–MeOH/CH_2Cl_2) of the residue and recrystallization from ethyl acetate gave 213 mg (51%) of the amide **21** as a white solid: mp 120–121 °C; IR (KBr) 3300, 1635, 1563, 1545 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.3 (m, 2 H), 7.0 (1 H, d, J = 8 Hz), 5.9 (br, 1 H), 3.4 (s, 3 H), 2.1 (s, 2 H); MS m/z 354 (M^+). Anal. ($C_{18}H_{24}Cl_2N_2O$) C, H, N.

X-ray Crystal Structure Determination. Single crystals of the amide **21** were obtained by recrystallization from ethyl acetate. The crystals were monoclinic with a = 8.353 Å, b = 18.674 Å, c = 23.588 Å, β = 96.24°, volume = 3658 Å^3, space group $P21/c$, $C_{18}H_{24}N_2Cl_2O$, M_r = 355.3, and a calculated density 1.290 g/cm^3. The crystal measured 0.4 × 0.3 × 0.1 mm. There were eight molecules per unit cell and two molecules per asymmetric unit. All measurements were done on a Phillips PW1100 diffractometer with Mo $K\alpha_1$ radiation (λ = 0.709 26 Å) using a graphite monochrometer. The $\theta/2\theta$ scan technique was used. Of the 5426 reflections which were taken with 2θ = 6–50°, 4662 unique reflections were observed ($I > 2\sigma(I)$). The structure was solved by direct methods (MULTAN 78). Block-diagonal least-squares refinement (BDLS) with anisotropic thermal factors for the 46 non-hydrogen atoms gave a refinement that converged at R = 0.101. For molecule B, all 24 hydrogen atoms were localized by a difference-Fourier synthesis. The disorder in molecule A necessitated the calculation of the location of its hydrogen atoms. The consideration of all the hydrogen atoms using the BDLS calculation improves the R factor to 0.085.

μ and δ Opiate Receptor Binding. Membrane suspensions were prepared from male Hartley (Elm Hill, Chelmsford, MA; animal code: Elm:(DH)) guinea pig (350–400 g) whole brains as previously described.[15,16] Whole brains minus cerebellum were dissected and homogenized with a Brinkman Polytron (setting 6, 20 s) in 10 volumes (w/v) of ice-cold 50 mM Tris·HCl buffer (pH 7.4 at 4 °C). The homogenate was centrifuged twice at 48000g for 10 min at 4 °C with rehomogenization of the pellet in fresh Tris·HCl buffer between centrifugations. The pellet was homogenized in 10 volumes of Tris·HCl buffer, incubated at 37 °C for 45 min to remove endogenous opiate-like substances, and centrifuged. The final pellet was homogenized in 150 volumes (based on original tissue weight) of 50 mM Tris·HCl buffer. In the binding assay, 1.0-mL aliquots of the final tissue suspension (equivalent to about 15 mg of original tissue) were added to triplicate tubes containing [^{3}H]DAGO (1.0 nM, specific activity 30–60 Ci/mmol, DuPont-NEN, μ-receptor binding), or [^{3}H]-D-Ala^2-D-Leu^5-enkephalin (DADLE) (1.0 nM, specific activity 30–60 Ci/mmol, DuPont NEN, δ-receptor binding) plus or minus the test compound to a final volume of 1.3 mL. Nonspecific binding was determined in the presence of 10 μM levallorphan. Tubes were incubated at 25 °C for 1 h and the contents were filtered under vacuum through Whatman GF/B glass fiber filters. Unbound radioactivity was removed with 3 × 4 mL washes with ice-cold Tris·HCl buffer, and the filters were placed in scintillation vials with 3.5 mL of scintillation cocktail. After equilibration, radioactivity determinations were made and data calculations were performed as described below.

κ-Receptor Binding. [^{3}H]Ethylketocyclazocine (EKC) was measured as previously described.[17] The tissue pellet used in this assay was prepared as described for the μ- and δ-receptor binding assays. In the binding assay, 1.0-mL aliquots of the final tissue suspension (equivalent to about 15 mg of original tissue) were added to triplicate tubes containing [^{3}H]EKC (final concentration 2.0 nM, specific activity 15–30 Ci/mmol, DuPont-NEN) plus or minus the test compound and 100 mM NaCl, 20 μM cold DADLE, and 20 μM morphiceptin (Peninsula Labs) in a final volume of 1.3 mL. Nonspecific binding was determined in the presence of 10 μM unlabeled EKC. Tubes were incubated at 25 °C for 45 min and the contents were filtered under vacuum through Whatman GF/B glass fiber filters. The filters were washed three times with 4.0-mL aliquots of ice-cold Tris·HCl buffer and placed in scintillation vials with 3.5 mL of scintillation cocktail. After equilibration, radioactivity determinations were made and the data calculations were performed as described below.

Data Analysis. The binding data from three separate experiments were analyzed simultaneously by nonlinear regression using RS/1 (RS/1 Release 2 Features, Bolt, Beranek and Newman Software Products Corp., Cambridge, MA 1985). The IC_{50} values generated by this analysis are expressed as the mean SEM.

Phenylquinone Writhing.[18] Male CF-1 (Charles River; animal code: Crl:CF1BR) mice (18–23 g) were housed under standard laboratory conditions prior to testing. Ten mice were used per dose of test compound which was administered subcutaneously with 3% corn starch as vehicle (0.2 mL). After 30 min, the mice received 3.75 mg/kg of phenylquinone in 5% aqueous ethanol injected intraperitoneally. The animals were immediately placed in observation cages, where they were allowed to move freely. If a stretching response was observed over a 10-min period, the compound was considered to be inactive.

Tail Flick.[19] Male CF-1 (Charles River; animal code: Crl:CF1BR) mice (18–23 g) were housed under standard laboratory conditions prior to testing. Animals were restrained by placement into metal cylindrical tubes (25 mm × 750 mm) designed to fit into the tail-flick apparatus, enabling the animals tail to protrude from the end for application of the nociceptive stimulation. A light source with a built-in parabolic reflector (Sylvania, DJL, 150 W), focused 5 cm below the tail of the mouse, was used to induce the tail-flick response. The intensity of the stimulus was adjusted so that untreated mice flicked their tails away from the heat source with a latency between 3.5 and 4.5 s. The animals were exposed to the nociceptive stimulus 30 min after the test compound was administered subcutaneously with 3% corn starch as the vehicle (0.2 mL). If the mouse had not flicked its tail within 10 s after application of the heat stimulus, the stimulus was terminated.

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Registry No. 4, 2038-57-5; **5**, 119907-56-1; (±)-**6**, 119878-55-6; (±)-**7**, 119878-11-4; (±)-**8**, 119878-12-5; (±)-**9**, 119878-13-6; (±)-**10**, 119878-14-7; (±)-11, 119878-15-8; (±)-**12**, 119878-16-9; (±)-**13**, 119878-17-0; (±)-**14**, 119878-18-1; (±)-**14**·HCl, 119878-39-6; (±)-**15**, 119878-19-2; (±)-**15**·HCl, 119878-40-9; (±)-**16**, 119878-20-5; (±)-**16**·HCl, 119878-41-0; (±)-**17**, 119878-21-6; (±)-**17**·HCl, 119878-42-1; (±)-**18**, 119878-22-7; (±)-**18**·$C_4H_4O_4$, 119878-43-2; (±)-**19**, 119878-23-8; (±)-**19**·HCl, 119878-44-3; (±)-**20**, 119878-38-5; (±)-**20**·$C_4H_4O_4$, 119907-54-9; (±)-**21**, 119878-24-9; (±)-**22**, 119878-25-0; (±)-**22**·HCl, 119878-45-4; (±)-**23**, 119878-26-1; (±)-**23**·$C_4H_4O_4$, 119878-46-5; (±)-**24**, 119878-27-2; (±)-**24**·$C_2H_2O_4$, 119907-55-0; (±)-**25**, 119878-28-3; (±)-**25**·HCl, 119878-47-6; (±)-**26**, 119878-29-4; (±)-**26**·$C_4H_4O_4$, 119878-48-7; (±)**27**, 119878-30-7; (±)-**27**·HCl, 119878-49-8; (±)-**28**, 119878-31-8; (±)-**28**·$C_4H_4O_4$, 119878-50-1; (±)-**29**, 119878-32-9; (±)-**29**·$C_4H_4O_4$, 119878-51-2; (±)-**30**, 119878-33-0; (±)-**30**·HCl, 119878-52-3; (±)-**31**, 119878-34-1; (±)-**31**·HCl, 119878-53-4; (±)-**32**, 119878-35-2; (±)-**33**, 119878-36-3; (±)-**33**·$C_4H_4O_4$, 119878-54-5; (±)-**33**(R_1 = H), 119878-10-3; (±)-**34**, 119878-37-4; (±)-**34** (R_1 = H), 119907-53-8; (±)-**35**, 21797-84-2; **36**, 119878-56-7; 2-BrC_6H_4COCl, 7154-66-7; 3-BrC_6H_4COCl, 1711-09-7; 4-BrC_6H_4COCl, 586-75-4; 4-ClC_6H_4COCl, 122-01-0; 4-FC_6H_4COCl, 403-43-0; 4-$MeOC_6H_4COCl$, 100-07-2; 3,4-$Cl_2C_6H_3COCl$, 3024-72-4; 3,4-$Cl_2C_6H_3CH_2CO_2H$, 5807-30-7; 4-$BrC_6H_4CH_2CO_2H$, 1878-68-8; $C_6H_5(CH_2)_2COCl$, 645-45-4; 4-$BrC_6H_4SO_2Cl$, 98-58-8; 4-$CH_3C_6H_4COCl$, 874-60-2; 4-$CF_3C_6H_4COCl$, 329-15-7; 3,4-$Br_2C_6H_3COCl$, 21900-35-6; 2-Cl, 4-BrC_6H_3COCl, 21900-55-0; 2-CH_3, 4-BrC_6H_3COCl, 21900-45-8; benzyl chloroformate, 501-53-1; ethyl chloroformate, 541-41-3.

Supplementary Material Available: Tables listing bond distances, bond angles, positional parameters for hydrogen and non-hydrogen atoms, and general displacement parameter expressions (5 pages). Ordering information is given on any current masthead page.

Synthesis and Thromboxane Synthetase Inhibitory Activity of Di- or Tetrahydrobenzo[*b*]thiophenecarboxylic Acid Derivatives

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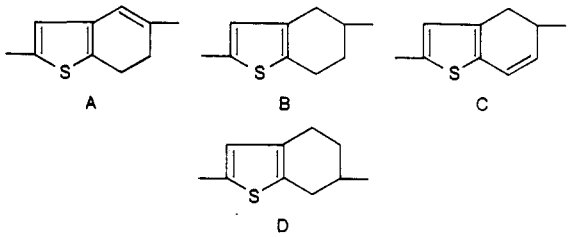
1-Imidazolylalkyl-substituted di- or tetrahydrobenzo[*b*]thiophenecarboxylic acid derivatives and related compounds were synthesized from tetrahydrobenzo[*b*]thiophene derivatives (1 or 4) in order to study the structure–activity relationships of the inhibition of thromboxane A_2 synthetase in vitro. Sodium 2-(1-imidazolylmethyl)-4,5-dihydrobenzo[*b*]thiophene-6-carboxylate (**26**) and 2-(1-imidazolylmethyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophene-6-carboxylic acid hydrochloride (**28**) showed the most potent and specific activity in vitro and in vivo for thromboxane A_2 synthetase inhibition.

In recent years, the interesting biological properties of thromboxane A_2 (TXA_2) synthetase inhibitors have been described.[1] Furthermore, such inhibitors have been found to be useful in the treatment or prevention of cardio- and cerebrovascular diseases.[2]

In 1977, Needleman[3] discovered that imidazole inhibited thromboxane synthetase, the enzyme that converts prostaglandin H_2 to the potent vasoconstrictor and platelet aggregating agent TXA_2. After this discovery, many compounds[1,4] having the imidazole (or pyridine) moiety were synthesized in the expectation of obtaining potent inhibitors. in many cases, the structural requirements for TXA_2 synthetase inhibitors possessing a high degree of selectivity are the presence of a carboxylic acid group and an imidazole moiety in a molecule. Furthermore, the distance between the imidazole and carboxylic acid groups has been found to be especially important for optimal potency.[1b,d]

On the basis of this knowledge, we turned our attention to the development of new TXA_2 synthetase inhibitors and to the synthesis of relatively rigid bicyclic compounds such as the dihydro- and tetrahydrobenzo[*b*]thiophenes (A–D).



Chemistry

The dihydrobenzo[*b*]thiophene derivatives possessing a carboxylic acid group at either the 5- or 6-position were synthesized as shown in Scheme I. Reaction of 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene (1)[5] with dimethyl carbonate in the presence of NaH gave carboxylate 2. Sodium borohydride ($NaBH_4$) reduction of 2 followed by

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