oxalate), recrystallized from EtOH: mp 188–190 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 6.57 (s, 2, aromatic *H*), 4.83 (br s, 2, O*H*), 3.3–1.0 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2CH_2), 0.89 (t, 3, CH_2). Anal. ($C_{21}H_{28}N_2O_6$) C, H, N.

2-(Cyanomethyl)-4-*n*-propyl-8,9-dihydroxy-1,2,3,4,4a,5,-6,10b-octahydrobenzo[*f*]quinoline (21d). A 73% yield of **21d** (as the oxalate) was obtained, recrystallized from EtOH: mp 212–214 °C; NMR (80 MHz) ($CDCl_3$) (free base) δ 7.16 (s, 2, aromatic *H*), 6.75–6.25 (m, 2, 2 O*H*), 4.1–1.0 (m, 17, C-1, C-2, C-3, C-4a, C-5, C-6, C-10b *H*, CH_2CN, NCH_2CH_2), 0.88 (t, 3, CH_3). Anal. ($C_{21}H_{28}N_2O_6$) C, H, N.

Dopamine Radioligand Binding Assay. Competition radioligand binding assays were performed by incubating bovine anterior pituitary membranes with the specific dopamine radioligand [^{3}H]spiroperidol (spiperone) (1.0–1.5 nM; sp act. 26.4 Ci/mmol; New England Nuclear) in the presence of increasing amounts of the indicated dopamine congeners (100 μM–0.1 nM, 19 concentrations). Membranes were prepared as previously described,[37] and the incubation was carried out at 23 °C for 60 min. The assay buffer employed consisted of 50 mM Tris, 120 mM NaCl, 5 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 0.1% ascorbic acid, and 12.5 μM nialamide (final pH 7.4). Membrane-bound [^{3}H]spiroperidol was separated from free by vacuum filtration through a Whitman GF/C glass fiber filter. Nonspecifically bound [^{3}H]spiroperidol was determined by performing parallel incubations in the presence of 1000-fold-excess of *d*-butaclamol (Ayerst), a potent dopamine agonist.

Competition curves were analyzed by an iterative, nonlinear least-squares curve-fitting procedure according to a one- or two-affinity-state model for ligand–receptor systems. This computer-assisted analysis provides estimates for the affinity of the congener for the different states of the receptor ($K_{i\,high}$ and $K_{i\,low}$) and the proportion of these states. The inhibition constant (K_i) was determined by the relationship: $K_i = IC_{50}/[1 + (L/K_D)]$,[42] where IC_{50} = competitor concentration which inhibited [^{3}H]-spiroperidol binding by 50%, L = concentration of [^{3}H]-spiroperidol used in the assay (1.0–1.5 nM) and K_D = the dissociation constant of [^{3}H]spiroperidol for its binding sites (0.16 nM). Statistical analysis comparing "goodness of fit" between the one- and two-affinity-state models was also performed and used to determine the appropriate model for the congener being examined.[43] An f value greater than 3.7 indicates statistical significance at the $p < 0.05$ confidence level.

Acknowledgment. Financial support from the U.S. Public Health Service is gratefully acknowledged (NIH Grant No. GM 31661 and AM 07256).

Registry No. **3a**, 33892-75-0; **3b**, 6836-19-7; **3c**, 24039-89-2; **3d**, 13575-75-2; **4a**, 60573-59-3; **4b**, 60573-58-2; **4c**, 52644-00-5; **4d**, 35491-96-4; **5a**, 95838-85-0; **6a**, 32940-15-1; **6b**, 4133-34-0; **6c**, 52644-01-6; **6d**, 2472-13-1; **9a**, 63307-15-3; **9b**, 33212-96-3; **10a**, 119530-27-7; **10a**·perchlorate, 119530-30-2; **10b**, 119530-28-8; **10b**·perchlorate, 119530-31-3; **10c**, 119530-29-9; **10c**·perchlorate, 119530-32-4; **10d**, 119567-30-5; **10d**·perchlorate, 119567-31-6; **11a**, 119530-33-5; **11a**·perchlorate, 119616-65-8; **11b**, 119530-34-6; **11b**·perchlorate, 119616-66-9; **11c**, 119530-35-7; **11c**·perchlorate, 119616-67-0; **11d**, 119530-36-8; **11d**·perchlorate, 119616-68-1; **12**, 119616-63-6; **13**, 119616-64-7; **14a**, 119530-37-9; **14a**·picrate, 119616-69-2; **14b**, 119530-38-0; **14b**·picrate, 119616-70-5; **14c**, 119530-39-1; **14c**·picrate, 119616-71-6; **14d**, 119530-40-4; **14d**·picrate, 119616-72-7; **15a**, 119530-41-5; **15a**·picrate, 119616-73-8; **15b**, 119567-32-7; **15c**, 119530-42-6; **15c**·picrate, 119616-74-9; **15d**, 119530-43-7; **16a**, 119530-44-8; **16a**·perchlorate, 119616-75-0; **16b**, 119530-45-9; **16b**·perchlorate, 119616-76-1; **17a**, 119530-46-0; **17a**·perchlorate, 119616-77-2; **17b**, 119530-47-1; **17b**·oxalate, 119616-78-3; **17c**, 119530-48-2; **17c**·picrate, 119616-79-4; **17d**, 119530-49-3; **17d**·oxalate, 119616-80-7; **18a**, 119530-50-6; **18a**·picrate, 119616-81-8; **18b**, 119530-51-7; **18b**·picrate, 119617-88-8; **18c**, 119530-52-8; **18c**·picrate, 119617-89-9; **18d**, 119530-53-9; **18d**·picrate, 119616-82-9; **19a**, 119530-54-0; **19a**·oxalate, 119616-83-0; **19b**, 119530-55-1; **19b**·oxalate, 119616-84-1; **20a**, 113528-14-6; **20a**·oxalate, 119616-85-2; **20b**, 113528-15-7; **20b**·oxalate, 119616-86-3; **20c**, 113528-18-0; **20c**·oxalate, 119616-87-4; **20d**, 113528-19-1; **20d**·oxalate, 119616-88-5; **21a**, 113528-16-8; **21a**·oxalate, 119616-89-6; **21b**, 113528-17-9; **21b**·oxalate, 119616-90-9; **21c**, 113540-43-5; **21c**·oxalate, 119617-90-2; **21d**, 113528-20-4; **21d**·oxalate, 119616-91-0; ethyl 3-(2′,3′-dimethoxyphenyl)propionate, 63307-08-4; ethyl 3-(3′,4′-dimethoxyphenyl)propionate, 5462-13-5; methyl 2-(bromomethyl)acrylate, 4224-69-5; propylamine, 107-10-8.

(40) Ferris, A. F. *J. Org. Chem.* **1955**, *20*, 780.
(41) Floss, H. G. Private communication.
(42) Cheng, Y.; Prusoff, W. H. *Biochem. Pharmacol.* **1973**, *22*, 3099.
(43) Rodbard, D.; Lenox, R. H.; Wrat, H. L.; Ramseth, D. *Clin. Chem.* **1976**, *22*, 350.

Synthesis and Pharmacological Evaluation of 4,4-Disubstituted Piperidines

John A. Colapret,* George Diamantidis,† H. Kenneth Spencer, Ted C. Spaulding,‡ and Frieda G. Rudo§

Anaquest Pharmaceuticals, BOC Technical Center, 100 Mountain Avenue, Murray Hill, New Jersey 07974, and University of Maryland, Baltimore College of Dental Surgery, 666 West Baltimore Street, Baltimore, Maryland 21201-1586.
Received June 6, 1988

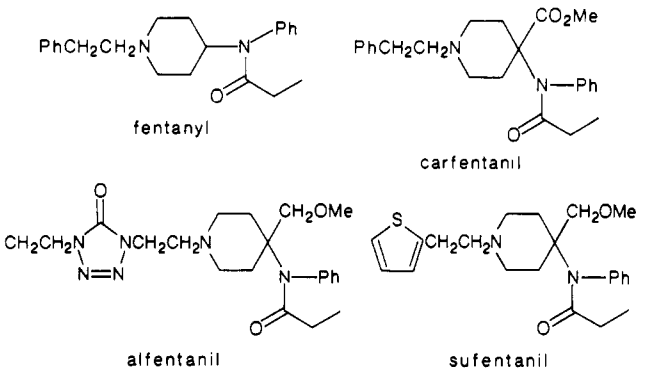
A new class of piperidine derivatives is added to the increasing family of compounds related to fentanyl and carfentanil. Herein, we describe the synthesis and pharmacology of a number of 1-(arylethyl)-4-(acylamino)-4-[(acyloxy)-methyl]piperidines such as **9**, **15**, and **23**. As expected, many of these congeners of fentanyl are extremely potent narcotic agonists. The aim of the study was to identify short-acting analgesic agents (i.e. less than 6 min in the mouse hot-plate assay) for possible use in the surgical theater. Many of the drugs proved to be of intermediate and long duration (i.e. 6–15 min and >15 min, respectively). In addition to analgesic activity, many of the compounds exhibited anesthetic properties as well. The structure–activity relationship for these entities is presented and discussed.

The accentuated interest in the piperidine class of opiate agonists continues to be expressed in the pharmaceutical community; the synthesis and biological properties of these agents have been the subject of ongoing investigations in these laboratories as well. Our focus has been directed toward the preparation of more complex molecular derivatives related to fentanyl, sufentanil, and carfentanil that would exhibit fewer deleterious side effects. The prototype fentanyl[1] was discovered some 25 years ago in the laboratories of Janssen et al.[2] and has been the major

* Author to whom correspondence should be addressed.
† Present address: Squibb Pharmaceuticals, New Brunswick, NJ 08903.
‡ Pharmacology Department, Anaquest.
§ University of Maryland.

(1) For a review of fentanyl and its pharmacology, see: Andrews, C. J. H.; Prys-Roberts, C. *Clinics in Anaesthesiology*; Vol. I, No. 1 Apr. 1983. W.B. Saunders Company Ltd.

0022-2623/89/1832-0968$01.50/0



contributor in the arena of intraveneous anesthesia agents. Significant developments have been made since then with regard to the molecular sophistication and clinical syndrome of these derivatives of piperidine—most notably, sufentanil[3] and alfentanil.[4] All these drugs exhibit the classic morphine syndrome—complete with respiratory depression and high addiction liability.[5] Our aim in this particular study was to examine a novel class of 4-carboalkoxy esters **9**, which were designed to undergo rapid metabolic inactivation and yield compounds with a short duration[6] of analgesia.

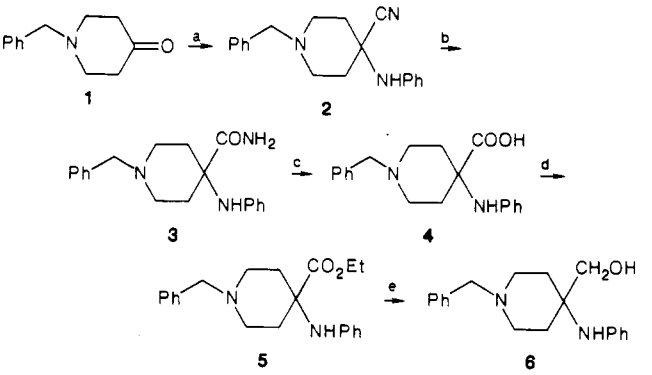
Chemistry

Several procedures for the preparation of the various intermediates (i.e. **2–5**) have been described.[2] The pathway for the synthesis of our pivotal starting material **6** is depicted in Scheme I and commences with the condensation of *N*-benzylpiperidone (**1**) with aniline in the presence of potassium cyanide (the Strecker synthesis) to afford the cyanoamine **2**.[2c]

Sequential hydrolysis was the most efficacious route to the amino acid **4**, although several "one-pot" methods were tried. In this event, the cyano amine **2** was subjected to sulfuric acid to afford the anilino amide **3**,[2b] which was further hydrolyzed to its corresponding acid **4**[2d] with concentrated hydrochloric acid at reflux. Several attempts to reduce this acid directly to the target alcohol **6** were thwarted. However, by esterification of the acid to give ethyl ester **5**[2d] and subsequent reduction (lithium aluminum hydride), high yields of the 4-(hydroxymethyl)-4-anilino-*N*-benzylpiperidine (**6**) were achieved on a routine basis.

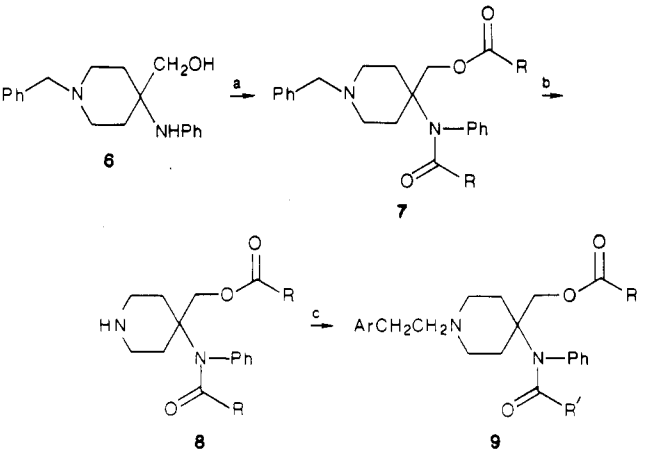
With quantities of the alcohol **6**[2a] in hand, preparation of the first series of compounds was straightforward (Scheme II). The hydroxyl and anilido nitrogen were acylated simultaneously by treatment of **6** with an excess of an acid halide (vida infra). The resulting ester amides **7** were then subjected to hydrogenolysis of the *N*-benzyl

Scheme I[a]



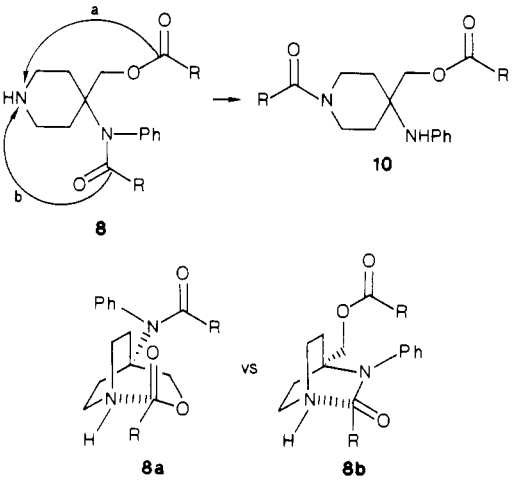
[a] Reagents: (a) KCN, $PhNH_2$; (b) H_2SO_4; (c) HCl (concentrated), reflux; (d) EtOH, toluene, reflux; (e) LAH, THF, 0 °C to room temperature.

Scheme II[a]



[a] Reagents: (a) RCOCl (2.5 equiv); (b) H_2, $Pd(OH)_2$-C; (c) $ArCH_2CH_2X$, KI, K_2CO_3, CH_3CN, reflux.

Scheme III



protecting group (hydrogen in the presence of Pearlman's catalyst), and the resulting secondary amines **8** were then N-alkylated with an appropriate arylethyl side chain to generate the free bases, **9**. For pharmacological screening, the oxalate salts were prepared.

One problem that complicated our plan was the tendency of the secondary piperidines **8** to suffer an intramolecular acyl-group migration (Scheme III) upon standing (either neat or in solution). In our compounds, the phenomena was first observed in NMR samples left overnight; however, analogous O to N acyl migrations has been well

(2) (a) Van Daele, P. G. H.; DeBruyn, M. F. L.; Boey, J. M.; Sanezuk, S.; Agten, J. T. M.; Janssen, P. A. J. *Arzneim.-Forsch. (Drug Res.)* **1976**, *26*(8), 1521. (b) Janssen, P. A. J.; et al. U.S. Patent 4,167,574, 1979. (c) Janssen, P. A. J.; et al. U.S. Patent 3,161,644, 1964. (d) Van Bever, W. F. M.; Niemegeers, C. J. E.; Janssen, P. A. J. *J. Med. Chem.* **1974**, *17*, 1047.

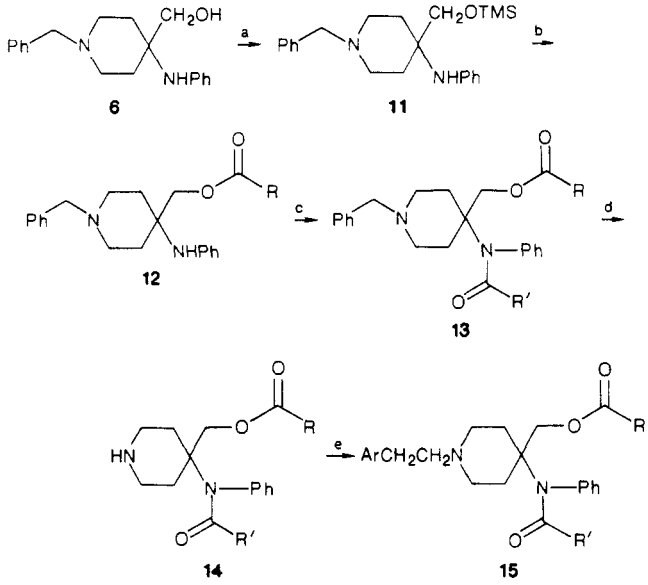
(3) (a) Mather, L. E. *Clin. Pharmacokinet.* **1983**, *8*, 422–446. (b) Van Bever, W. F. M.; Schellekens, K. H. L.; Niemegeers, C. J. E.; Janssen, P. A. J. *Arzneim.-Forsch. (Drug Res.)* **1976**, *26*(8), 1551.

(4) (a) Niemegeers, C. J. E.; Janssen, P. A. J. *Drug Dev. Res.* **1981**, *1*, 83–88. (b) Janssenns, F.; Tarremans, J.; Janssen, P. A. J. *J. Med. Chem.* **1986**, *29*, 2290.

(5) For a discussion of the clinical uses of these anesthetics, see: Janssen, P. A. J. *ACTA Anaesth. Scand.* **1982**, *26*, 262–8.

(6) We have defined the analgesic effect of a compound to be short acting if the duration is less than 6 min, intermediate if between 6 and 15 min, and long for times greater than 15 min.

Scheme IV[a]

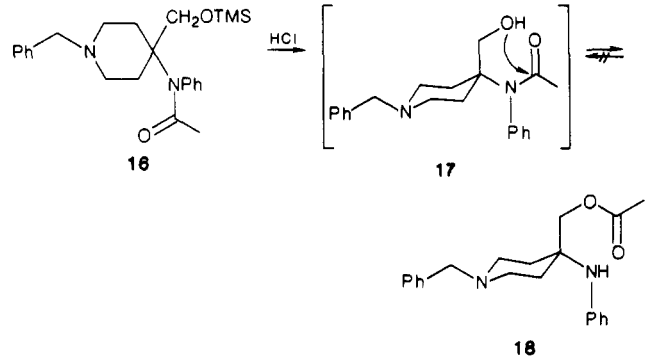


[a] Reagents: (a) TMSCl, CH_2Cl_2, 0 °C to room temperature; (b) RCOCl, then 1 N HCl, room temperature; (c) R'COCl; (d) H_2, $Pd(OH)_2$-C; (e) $ArCH_2CH_2X$, KI, K_2CO_3, CH_3CN, reflux.

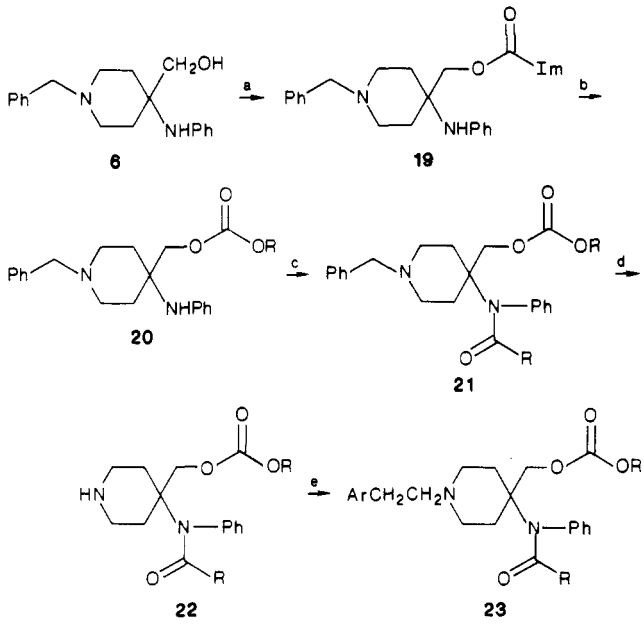
precedented in prodine derivatives.[7] Within this particular family of ester amides, two pathways are possible, but of these two, migration from the ester (path a) via a seven-membered transition state **8a** is the less likely when compared to the six-membered transition state **8b** (path b) available from the amide. This notion is supported in those cases where the two acyl groups are mixed (e.g. **1d**: R = Me; R' = Et). Clean migration of the propionyl group from the anilido nitrogen occurred while the ester functionality remained intact (N to N). It is noteworthy that this molecular rearrangement can be a major competing side reaction that renders the adducts such as **10** unsuitable for the subsequent substitution of the *N*-alkyl side chain. Nevertheless, this minor inconvenience could be avoided by simply carrying the free amine **8** (without purification) immediately to the N-alkylation step.

While the routes to the aforementioned bis-acylated adducts (i.e. R = R') proved to be straightforward, the preparation of the mixed ester amides (R ≠ R') was more convoluted (Scheme IV). In this mixed esteramide series (R ≠ R'), an effort was made to selectively acylate the hydroxyl group of **6** in the presence of the anilido nitrogen. Unfortunately, under a variety of conditions and with a number of acylating agents, this strategy was unsuccessful. Usually mixtures of monoacylated (both esters and amides were formed) and diacylated adducts were obtained. We then resorted to the alternative strategy of protecting the alcohol of **6** as its trimethylsilyl ether **11**, acylating the anilido nitrogen, and unmasking the hydroxyl group to afford compounds of the type **17** (Scheme V). In this sequence of reactions, protection of the alcohol was routine as was the subsequent acylation to prepare the derivatives **16**. However, it was during the hydrolysis of the *O*-trimethylsilyl ether **16** that yet another acyl group migration was encountered (Scheme V), i.e. from the anilido nitrogen to the free hydroxyl group via **17**. Hydroxymethyl intermediates of this type can be isolated, but they undergo the acyl migration (**17** to **18**) as easily as the aforementioned

Scheme V



Scheme VI[a]



[a] Reagents: (a) Im_2CO; (b) ROH, HCl (cat.), room temperature; (c) RCOCl; (d) H_2, $Pd(OH)_2$-C; (e) $ArCH_2CH_2X$, KI, K_2CO_3, CH_3CN, reflux.

examples. However, this rearrangement affords a viable pathway to the esters **12** and **18** for it is general and thermodynamically favored. We verified this by isolating ester **18**, resubjecting this material to the hydrolysis conditions (1 N HCl at room temperature), and recovering it unchanged. Prolonged exposure (>24 h) of **18** to these reaction conditions eventually led to hydrolysis of the ester. Thus, the concise procedure for the transformation of **16** to **18** was to treat the acylated *O*-trimethylsilyl ether with 1 N HCl at room temperature overnight. This chemistry thus accomplished the desired synthetic goal of selective acylation of alcohol **6**. With the differentiated acyl groups in place, the synthesis was completed as described above: hydrogenolysis of the benzyl group to give the secondary amines **14** followed by N-alkylation with an arylethyl side chain, thus affording the mixed ester amides **15**.

An interesting discovery led to the preparation of another set of compounds whose synthesis in a direct fashion was precluded, once again by lack of O vs N selectivity. Specifically, attempts to prepare carbonate derivatives (such as **20**) directly by the action of chloroformates upon the alcohol **6** were impeded not only by the lack of selectivity (N vs O acylation) but the deleterious side reaction of N-debenzylation as well. We overcame these problems by utilizing a mild two-step procedure (Scheme VI). The novel urethane **19** was prepared by the condensation of **6** with 1,1'-carbonyldiimidazole (Im_2CO), and under these

(7) (a) Abdel-Monem, M. M.; Larson, D. L.; Kupferberg, H. J.; Portoghese, P. S. *J. Med. Chem.* **1972**, *15*, 494. Abdel-Monem, M. M.; Harris, P. A.; Portoghese, P. S. *J. Med. Chem.* **1972**, *15*, 706.

conditions, we obtained only the monocondensed adduct. It was subsequently discovered that treatment of **19** with a simple alcohol (in the presence of catalytic acid) was sufficient to arrive at carbonates **20** in good yields. Acylation of the anilido nitrogen then afforded the carbonates **21**, which were subjected to hydrogenolysis, and the resulting secondary amines **22** were alkylated with an arylethyl side chain.

The synthetic schemes described above allowed the preparation of the desired 4,4-disubstituted piperidines, and the final products with their biological properties are depicted in Table I. The arylethyl side chains were chosen to enhance the drugs' lipophilicity, and the overall pharmacological profile of these piperidines is presented and discussed below.

Pharmacology

The analgesic properties of these compounds were evaluated by the standard mouse hot-plate assay (vida infra) using doses from 1 mg/kg to 5 mg/kg as the testing range. A compound was considered inactive if it produced less than 100% analgesia at the 5 mg/kg dose; it was defined as a convulsant if spasmodic motions were noted at the 1 mg/kg dose. The duration of analgesia was also determined and we have defined a compound to be short acting (S) if the effect is less than 6 min and intermediate (I) if between 6 and 15 min and long duration (L) is anytime greater than 15 min (see the Experimental Section).

The anesthesic effects of these drugs were evaluated by the loss of righting (LOR) subsequent to a bolus injection of the compound. The least effective dose to anesthetize 100% (LED_{100}) of the animals was determined, and the duration of anesthesia was the time from injection to righting of the animals.

The in vitro assay involved the displacement of [^{3}H]-naloxone from freshly prepared rat brain homoganates. The K_i was determined from triplicate runs at doses of 1, 10, and 100 nM and calculated according to the method of Cheng and Prusoff.[14] A summary of all these biological properties is displayed in Table I.

Results and Discussion

The choice of the *N*-arylethyl substituent was dictated by literature precedent[2-4] and was patterned after the substitutions in fentanyl, alfentanil, etc. The corresponding *N*-benzyl analogues (e.g. **7** and **13**) were also screened and found to be devoid of analgesic and anesthetic activity. Within the series of arylethyl side chains, the phenethyl and the thienylethyl substituents were found to be more effective as analgesic agonists while the tetrazolo, tetrazo, and the phthalimido derivatives were all of diminished potency and did not displace [^{3}H]naloxone from the opiate receptor site. Surprisingly, several of these derivatives were weak anesthetic agents (**3c**, **4b,c**, **5b,f**), but since they produced tremors and convulsions during screening, further study was not persued. The thienylethyl derivatives (**2a–j**) were generally found to be more potent analgesics and of shorter duration than their corresponding phenethyl analogues (**1a–j**).

Several trends are apparent with respect to the nature of the ester and amide substituents (R and R′). As a general rule, lengthening or branching of either the amide or the ester leads to diminished potency (**1f,g,j,k** and **2f,g,j,k**) and increased duration of analgesia compared to fentanyl. This trend could be a consequence of increasing resistance in the breakdown of more sterically encumbered esters and amides, and in the case of the diphenyl congeners (**1c** and **2c**) insolubility precluded comparable testing. However, while it is advantageous to restrict the alkyl groups to sterically smaller substituents (Me, Et, OMe, and OEt), there are dramatic differences in activity even within these series. We focus the following discussion on the compounds **1d,e,h,i** and **2d,e,h,i**.

An examination of four active congeners in the *N*-phenethyl series reveals that the mere transposition of acetyl for propionyl groups (**1d** vs **1e**) imparts a decrease in analgesic activity (relative to fentanyl) with a 14-fold decrease in receptor binding affinity (K_i), but the two are similar to each other in their anesthesic properties, i.e. same approximate potency, 5–6 min duration. The same trend was also observed for the thienylethyl series (**2d** and **2e**) with respect to their analgesic properties. However, the duration of anesthesia was only 1.5 min for **2d** while **2e** was 4 times longer (6.3 min).

We were keenly interested in the carbonate derivatives (**1h,i** and **2h,i**); we rationalized that their increased chemical lability (aqueous hydrolysis) should have rendered them more susceptible to enzymatic breakdown to afford their inactive hydroxymethyl counterparts.[8] This reasoning was not expressed in the analgesic component of the drugs but was evident in their anesthetic properties. This group of carbonates showed interesting trends: although change from a methyl to an ethyl carbonate (**1i** and **2i** vs **1h** and **2h**) led to diminished analgesic activity, the most surprising finding was the long duration of this analgesia in spite of the increased chemical sensitivity of the labile substituent. These results suggest that a hydrolytic mechanism for the breakdown of these species is, at best, very slow. Furthermore, on the basis of their relatively strong binding constant (in vitro), we speculate that the duration could be due to a strong interaction of the drug with the active site(s) or the carbonates may be poor metabolic substrates. All eight compounds were anesthetics and displayed a similar range of potency (LED_{100} = 15.5 mg/kg). That analgesia and anesthesia do not necessarily parallel each other is nicely demonstrated in the case of **2h**. This carbonate proved to be a potent analgetic with a long duration (34.1 min to 50% maximum percent effect, MPE), yet as an anesthetic, it was the shortest acting (0.83 min) in the entire study.

While the duration of anesthetic action for many of these compounds was longer than we had hoped, the synthetic effort uncovered several potent narcotic agonists and expanded the scope of the structure–activity relationship of 4,4-disubstituted piperidines.

Experimental Section

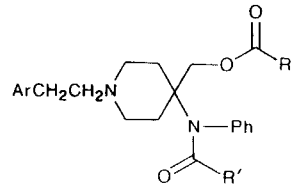
Melting points were recorded on a Thomas-Hoover melting point apparatus and are uncorrected. ^{1}H NMR were recorded on a Varian EM 360 (60 mHz) or IBM NM 270 (270 mHz) spectrometer as solutions in deuterated chloroform. Chemical shifts are reported in δ downfield from the internal standard, tetramethylsilane. Singlet, broad singlet, doublet, triplet, and multiplet are abbreviated as s, br s, d, t, and m, respectively. *J* stands for the coupling constant measured in hertz (Hz). High-resolution mass spectra were obtained on a Hewlett-Packard Model 5995 gas chromatograph/mass spectrometer. Analyses were performed by the Analytical Services division, BOC Technical Center, Murray Hill, NJ.

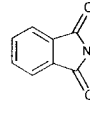
Chromatographic separations were carried out on silica gel by using "flash" technique.[9] Other preparative chromatography was performed on a Waters Associates Prep 500 System using two Prep PAK silica gel columns.

(8) Unpublished results from these laboratories: In our hands, many 4-(hydroxymethyl)piperidines have been screened, and all these derivatives have shown either diminished activity or no analgesic activity.

(9) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

Table I. Chemical and Biological Properties of 4,4-Disubstituted Piperidines



Ar	entry	R	R′	yield,[a] %	mp, °C	analysis (oxalates)	K_i, nM	ED_{50}[c]	mouse hot plate (analgesia assay): duration[d]	loss of righting (anesthesia assay) LED_{100}[e]	loss of righting (anesthesia assay) duration, min
	1a	Me	Me	78	190–3	($C_{26}H_{32}N_2O_7$) C, H, N	11.5	0.317 (0.198–0.510)	L	inactive	
	1b[b]	Et	Et	22	182	Janssen				ref 3a	
	1c	Ph	Ph	88	183–5	($C_{36}H_{36}N_2O_7$) C, H, N	insol	inactive		inactive	
	1d	Me	Et	68	169–73	($C_{27}H_{34}N_2O_7$) C, H, N	3.49	0.055 (0.041–0.075)	L	10.0	5.2
	**1e**	Et	Me	90	165–8	($C_{27}H_{34}N_2O_7$) C, H, N	49.4	0.487 (0.408–0.582)	L	15.5	6.5
	1f	nPr	nPr	61	150–2	($C_{30}H_{40}N_2O_7$) C, H, N	24.4	inactive		inactive	
	1g	iPr	iPr	62	140–2	($C_{30}H_{40}N_2O_7$) C, H, N	7.68	0.108 (0.069–0.169)	L	15.5	2.0
	1h	OEt	Et	54	163–5	($C_{28}H_{36}N_2O_8$) C, H, N	9.95	0.058 (0.041–0.075)	L	15.5	3.3
	1i	OMe	Et	72	162–5	($C_{28}H_{36}N_2O_8$) C, H, N	9.95	0.058 (0.041–0.075)	L	15.5	3.3
	ij	tBu	Et	62	186–8	($C_{27}H_{34}N_2O_8$) C, H, N ($C_{30}H_{40}N_2O_7$) C, H, N	29.8	inactive		40.0	4.0
	1k	CH(OMe)Me	CH(OMe)Me	56	125–8	($C_{30}H_{40}N_2O_9 \cdot 1.5H_2O$) C, H, N	>100	inactive		25.0	5.3
	2a	Me	Me	84	183–4	($C_{24}H_{30}N_2O_7S$) C, H, N	13.95	0.472 (0.395–0.564)	I	15.5	3.2
	2b	Et	Et	64	173–5	($C_{26}H_{34}N_2O_7S$) C, H, N	13.8	0.036 (0.257–0.505)	L	15.5	3.5
	2d	Ph	Ph	92	173–5	($C_{34}H_{34}N_2O_7S \cdot 0.25H_2O$) C, H, N	insol	inactive		inactive	
	2d	Me	Et	34	168–72	($C_{25}H_{32}N_2O_7S$) C, H, N	25.9	0.343 (0.249–0.473)	L	25.0	6.3
	**2f**	nPr	nPr	61	155–7	($C_{28}H_{38}N_2O_7S \cdot 0.25H_2O$) C, H, N	8.22	0.098 (0.074–0.127)	L	25.0	6.3
	2g	iPr	iPr	56	164–6	($C_{28}H_{38}N_2O_7S$) C, H, N	27.14	0.50 (0.38–0.65)	L	20.0	2.0
	2h	OEt	Et	40	179–81	($C_{26}H_{34}N_2O_7S$) C, H, N	9.1	0.06 (0.04–0.09)	L	15.5	0.83
	2i	OMe	Et	34	178–80	($C_{25}H_{32}N_2O_8S$) C, H, N	30.2	0.009 (0.007–0.012)	I	15.5	4.0
	2j	tBu	Et	39	172–4	($C_{28}H_{38}N_2O_7S \cdot 1.5H_2O$) C, H, N	40.5	inactive		63.0	11.0
	2k	CH(OMe)Me	CH(OMe)Me	36	115	($C_{28}H_{28}N_2O_9S$) C, H, N	>100	inactive		inactive	
	**3a**	Et	Et	62	160–3	($C_{25}H_{36}N_6O_8$) C, H, N	>100	inactive		inactive	
	3b	Me	Et	67	156–8	($C_{24}H_{34}N_6O_8 \cdot 0.25H_2O$) C, H, N	>100	inactive		inactive	
	3c	iPr	iPr	87	163–5	($C_{27}H_{40}N_6O_8$) C, H, N	>100	inactive		31.6	2.5
	3d	OMe	Et	72	156–9	($C_{24}H_{34}N_6O_9$) C, H, N	>100	inactive		convulsant @ 100 mg	
	4a	Me	Et	75	155.8	($C_{22}H_{30}N_6O_7 \cdot 0.25H_2O$) C, H, N	>100	inactive		convulsant @ 100 mg	
	4b	nPr	nPr	82	168–70	($C_{25}H_{36}N_6O_7$) C, H, N	55.6	inactive		40.0	3.0
	**4c**	iPr	iPr	88	168–70	($C_{25}H_{36}N_6O_7$) C, H, N	>100	inactive		40.0	2.0
	4d	tBu	Et	71	179–81	($C_{25}H_{36}N_6O_7$) C, H, N	>100	inactive		inactive	
	4e	OEt	Et	66	165–8	($C_{23}H_{32}N_6O_8$) C, H, N	>100	inactive		63.0	1.7
	4f	OMe	Et	61	149–53	($C_{22}H_{30}N_6O_8$) C, H, N	>100	inactive		inactive	
	5a	Et	Et	63	120–3	($C_{30}H_{35}N_3O_9$) C, H, N	>100	inactive		convulsant @ 15.5 mg	
	5b	Me	Et	72	126–9	($C_{29}H_{33}N_3O_9$) C, H, N	>100	inactive		convulsant @ 40 mg	
	**5c**	nPr	nPr	90	158–60	($C_{32}H_{39}N_3O_9$) C, H, N	>100	inactive		inactive	
	5d	iPr	iPr	86	122–4	($C_{32}H_{39}N_3O_9$) C, H, N	>100	inactive		inactive	
	5e	tBu	Et	92	160–2	($C_{32}H_{39}N_3O_9 \cdot 0.25H_2O$) C, H, N	>100	inactive		inactive	
	5f	OEt	Et	75	163–5	($C_{30}H_{35}N_3O_{10}$) C, H, N	>100	inactive		convulsant @ 25 mg	
	5g	OMe	Et	84	171–4	($C_{29}H_{33}N_3O_{10} \cdot 1.5H_2O$) C, H, N	>100	inactive		convulsant @ 100 mg	
	5h	CH(OMe)Me	CH(OMe)Me	50	131–5	($C_{32}H_{39}N_3O_{11} \cdot 1.5H_2O$) C, H, N	>100	inactive		convulsant @ 100 mg	
						fentanyl	2.16	0.018 (0.009–0.037)	I	6.0	3.16
						sufentanil	0.02	0.034 (0.185–0.0546)	I	15.5	3.2
						alfentanil	8.21	0.045 (0.022–0.068)	S	25.0	0.2

[a] Yields are for isolated purified bases (after the N-alkylation step), but are not optimized. [b] First reported by the laboratories of Janssen (ref 3a). [c] ED_{50} for mouse hot plate with 95% confidence limits; inactive refers to doses up to 5 mg/kg. [d] Duration of analgesia in the MHP (S = less than 6 min, I = between 6 and 15 min, L = greater than 15 min). [e] Least effective dose to anesthesitize 100% of animals; inactive for doses up to 100 mg/kg.

All experiments involving air-sensitive reagents were executed under an atmosphere of dry nitrogen. The glassware was oven-dried and heated in a nitrogen stream prior to use. Methylene chloride and triethylamine were distilled from calcium hydride. The acid chlorides were also freshly distilled from calcium hydride prior to use. The trimethylsilyl chloride was distilled from *N*,*N*-dimethylaniline prior to use. For pharmacological screening, the oxalate salts were prepared by stirring a solution of the base (in 2-propanol) with excess oxalic acid at room temperature and recrystallizing the solids to analytical purity. One compound representative of each class is presented below.

***N*-Benzyl-4-carbethoxy-4-anilinopiperidine (5).** A slurry of acid **4** (155 g, 0.50 mol) in a mixture of ethanol–toluene (1 L of 70:30) was heated at reflux for 10 days while the azeotrope was collected via a Dean–Stark trap. The trap was drained periodically till the pot volume was approximately half its original volume. The mixture was cooled to 0 °C whereupon 10% sodium hydroxide (250 mL) was added dropwise with stirring. The resulting slurry was extracted with methylene chloride (3 × 200 mL), and the combined organic layers were washed with brine (2 × 500 mL), dried ($MgSO_4$), and concentrated in vacuo to give a brown oil, which was further purified by flash column chromatography (2:1 hexane–ethyl acetate on silica gel; R_f 0.4) to afford 135 g (80%). NMR: δ 7.71 (s, 5 H), 7.14–6.35 (complex, 5 H), 4.05 (q, 2, H, J = 7 Hz), 3.47 (s, 3 H), 2.65–1.87 (complex, 8 H), 1.05 (t, 3 H, J = 7 Hz).

***N*-Benzyl-4-(hydroxymethyl)-4-anilinopiperidine (6).** To a mechanically stirred slurry of lithium aluminum hydride (7.99 g, 210.9 mmol) in dry THF (700 mL) at 0 °C was added dropwise a solution of ester **5** (47.6 g, 140.6 mmol) in dry methylene chloride (100 mL). The stirring was continued as the slurry warmed to room temperature overnight. TLC (silica gel, EtOAc) of an aliquot indicated complete consumption of the starting material. The mixture was worked up according to the procedure described in Feiser and Feiser[10] and, upon removal of the solvents, afforded 39.37 g (95%) as a pale yellow oil which was used without further purification. NMR: δ 7.40 (s, 5 H), 7.29–6.69 (complex, 5 H), 3.67 (s, 3 H), 3.50 (s, 3 H), 2.98–1.58 (complex, 8 H).

***N*-Benzyl-4-(acetoxymethyl)-4-acetanilidopiperidine (7) (Illustrated for R = Me).** To a stirred solution of alcohol **6** (2.96 g, 10.0 mmol) in dry methylene chloride (50 mL) at 0 °C was added freshly distilled acetyl chloride (1.72 g, 22.0 mmol), and stirring was continued overnight. TLC (EtOAc, silica gel) indicated complete consumption of the starting alcohol, and the solution was treated with 10% aqueous sodium hydroxide (50 mL). The resulting mixture was extracted with methylene chloride (3 × 75 mL), and the combined organic layers were dried ($MgSO_4$) and then concentrated in vacuo to afford a brown oil which was further purified by flash column chromatography (EtOAc–hexane 7:3) to give 2.43 g (64%) of pure **7** (R = Me).

4-(Acetoxymethyl)-4-acetanilidopiperidine (8) (Illustrated for R = Me). A mixture of ester amide **7** (R = Me) (3.80 g, 10.0 mmol) and palladium hydroxide on carbon (ca. 200 mg; Pearlman's catalyst) in ethanol (50 mL of 95%) was shaken under a hydrogen atmosphere (55–60 psi) at 50 °C for 2 h. TLC (EtOAc, silica gel) indicated complete consumption of the starting material, and the slurry was filtered. The filtrate was concentrated in vacuo to give a colorless oil which was dissolved in methylene chloride (75 mL) and washed with 10% sodium hydroxide (2 × 75 mL), dried ($MgSO_4$), and concentrated to afford 2.84 g (98%) of a colorless oil, which was used immediately for the next step.

***N*-(β-Arylethyl)-4-(acetoxymethyl)-4-acetanilidopiperidine (9) (Illustrated for Ar = Ph and R = R′ = Me).** To a stirred slurry of the secondary base **8** (2.90 g, 10.0 mmol), potassium carbonate (5.52 g, 20.0 mmol), and potassium iodide (840 mg, 5.0 mmol) in dry acetonitrile (30 mL) was added (2-bromoethyl)benzene (2.78 g, 15.0 mmol), and the resulting slurry was heated at reflux for 18 h. The mixture was cooled to room temperature and diluted with water (100 mL) to dissolve the solids, and the mixture was extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a brown oil which was further purified by flash column chromatography (EtOAc–hexane 7:3) to afford 3.07 g (78%) of a pale yellow oil.

***N*-Benzyl-4-[[(trimethylsilyl)oxy]methyl]-4-anilinopiperidine (11).** To a stirred solution of alcohol **6** (2.96 g, 10.0 mmol) in dry methylene chloride (30 mL) at 0 °C was added freshly distilled trimethylsilyl chloride (1.08 g, 10.0 mmol), and the resulting solution was warmed to room temperature overnight (18 h). The yellow solution was diluted with methylene chloride (100 mL) and washed with ammonium chloride (2 × 100 mL, saturated), dried ($MgSO_4$), and concentrated in vacuo to give a yellow oil which was further purified by flash column chromatography (EtOAc hexane 7:3) to afford 3.49 g (95%) of pure **11**. NMR: δ 7.70 (s, 5 H), 7.45–6.85 (m, 5 H), 3.81 (s, 2 H), 3.63 (br s, 3 H), 2.95–2.67 (m, 4 H), 2.25–2.05 (m, 4 H), 0.2 (s, 9 H).

***N*-Benzyl-4-(acetoxymethyl)-4-anilinopiperidine (12).** To a stirred solution of silyl ether **11** (3.68 g, 10.0 mmol) in dry methylene chloride (30 mL) at 0 °C was added freshly distilled acetyl chloride (970 mg, 10.0 mmol), and the resulting solution was warmed to room temperature overnight (18 h). Although intermediates of the type **16** could be isolated at this stage, the resulting oil was stirred with 1 N hydrochloric acid (50 mL) for 18 h, and the mixture was extracted with methylene chloride (3 × 100 mL). The combined organic layers were washed with water (2 × 100 mL), dried ($MgSO_4$), and concentrated in vacuo to give a brown oil which was purified by flash column chromatography (EtOAc–hexane 7:3) to afford 2.66 g (88%) of **12** (R = Me). NMR: δ 7.30 (s, 5 H), 7.45–6.55 (m, 5 H), 4.01 (s, 2 H), 3.49 (br s, 2 H), 2.58–2.18 (m, 4 H), 1.90 (s, 3 H), 1.98–1.54 (m, 4 H).

***N*-Benzyl-4-(acetoxymethyl)-4-propananilidopiperidine (13) (Illustrated for R = Me and R′ = Et).** To a stirred solution of ester **12** (2.96 g, 10.0 mmol) in dry methylene chloride (50 mL) at 0 °C was added freshly distilled propionyl chloride (1.72 g, 22.0 mmol), and then stirring was continued overnight (18 h). TLC (EtOAc, silica gel) indicated complete consumption of the starting ester, and the solution was treated with 10% aqueous sodium hydroxide (50 mL). The resulting mixture was extracted with methylene chloride (3 × 75 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated in vacuo to afford a brown oil which was purified by flash column chromtography to give 3.35 g (87%) of pure product. NMR: δ 7.50 (s, 5 H), 7.45–6.55 (m, 5 H), 5.05 (s, 2 H), 4.15 (q, 2 H, J = 7.0 Hz), 3.49 (br s, 2 H), 2.35 (s, 3 H), 3.09–1.63 (complex, 8 H), 1.01 (t, 3 H, J = 7.0 Hz).

***N*-Benzyl-4-[[(imidazolylcarbonyl)oxy]methyl]-4-anilinopiperidine (19).** To a stirred solution of alcohol **6** (2.96 g, 10.0 mmol) in dry methylene chloride (50 mL) at 0 °C was added 1,1′-carbonyldiimidazole (1.78 g, 11.0 mmol) as a solution in methylene chloride (5 mL). The resulting yellow solution was stirred at room temperature for 18 h, at which time it was washed with water (3 × 50 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford 3.20 g (82%) of a pale yellow oil. NMR: δ 8.08 (s, 1 H), 7.35 (s, 5 H), 7.08 (s, 1 H), 7.01–6.62 (m, 4 H), 4.48 (s, 2 H), 3.50 (s, 2 H), 3.45 (br s, 1 H), 2.80–2.42 (m, 4 H), 2.13–1.75 (m, 4 H).

***N*-Benzyl-4-[[(alkoxycarbonyl)oxy]methyl]-4-anilinopiperidine (20).** To a stirred solution of carbamate **19** (1.95 g, 5.0 mmol) in 5 mL of alcohol (either methanol or ethanol) was added a drop of 1 N hydrochloric acid and the stirring was continued overnight. The solution was diluted with methylene chloride (75 mL) and was washed with water (3 × 75 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford the corresponding carbonates.

***N*-(Phenylethyl)-4-[(carbomethoxyoxy)methyl]-4-(*N*-propionanilido)piperidine (1i)**: eluant EtOAc. NMR: δ 7.47 (s, 5 H), 7.28 (s, 5 H), 5.05 (s, 2 H), 3.84 (s, 3 H), 3.06–1.58 (complex, 14 H), 0.91 (t, 3 H, J = 6.0 Hz).

***N*-(2-Thien-2-ylethyl)-4-[(carbethoxyoxy)methyl]-4-(*N*-propionanilido)piperidine (2h)**: eluant EtOAc–hexane 3:1. NMR: δ 7.43 (s, 5 H), 7.29–6.70 (m, 3 H), 4.98 (s, 2 H), 3.80 (t, 3 H, J = 6.0 Hz), 3.21 (t, 3 H, J = 6.0 Hz), 3.16–1.53 (complex, 8 H), 1.24 (t, 3 H, J = 6.0 Hz), 0.98 (t, 3 H, J = 6.0 Hz).

***N*-[2-(4,5-Dihydro-5-oxotetrazol-1-yl)ethyl]-4-(acetoxymethyl)-4-(*N*-propionanilido)piperidine (3b)**: eluant EtOAc. NMR: δ 7.42 (s, 5 H), 4.92 (s, 2 H), 4.28–3.80 (m, 4 H), 2.98–1.17 (complex, 12 H), 2.14 (s, 3 H), 1.40 (t, 3 H, J = 6.0 Hz), 0.89 (t, 3 H, J = 6.0 Hz).

(10) Feiser and Feiser *Reagents for Organic Synthesis*; J. Wiley & Sons: New York, 1967; Vol. I, p 583.

N-(2-Tetrazol-2-ylethyl)-4-[(carbomethoxyoxy)methyl]-4-(N-propionanilido)piperidine (4f): eluant EtOAc. NMR: δ 8.53 (s, 1 H), 7.37 (br s, 5 H), 4.98 (s, 2 H), 4.81–4.55 (m, 2 H), 3.84 (s, 3 H), 3.14–1.28 (complex, 12 H), 0.85 (t, 3 H, J = 7.0 Hz).

N-(Phthalamidoethyl)-4-[(propionyloxy)methyl]-4-(N-propionanilido)piperidine (5a): eluant EtOAc–hexane 3:2. NMR: δ 7.90 (br s, 4 H), 7.42 (br s, 5 H), 4.98 (br s, 2 H), 3.71 (t, 3 H, J = 6.0 Hz), 2.85–1.62 (complex, 14 H), 1.47–0.92 (m, 6 H).

Pharmacological Methods. Mouse Hot-Plate Determination of ED_{50} Dose. Ten male Swiss-Webster mice, weighing 18–26 g, purchased from Hilltop Laboratories were utilized. Animals were randomly selected and allowed to acclimate to the laboratory environment for at least 1 h prior to testing. Drugs were injected iv in the lateral tail vein. The animal was placed on a hot plate kept at constant temperature (55.0 ± 0.5 °C) and observed for occurrence of licking of hind or front paws.

A timer was simultaneously started as the animal was placed on the hot plate and stopped when a nociceptive response was elicited. The animal was immediately removed from the hot plate and the latency time was recorded. Mice control latency times in excess of 15 s were eliminated from the study.

Test latency times were determined 5 min after iv administration of the test drug. Analgesia is defined as test hot plate latency of 2 or more times greater than control latency times. No animal was permitted to remain on the hot plate longer than 30 s to prevent tissue damage. The number of mice exhibiting analgesia out of 10 was plotted as a percentage affected, thus generating a dose–response curve. At least three doses between 10 and 90% of responding animals were utilized. ED_{50} values with 95% confidence limits were calculated.[11]

Duration of Analgesia. Two times the ED_{50} dose was administered to 10 mice, and the hot-plate latencies were determined at various times after injection of the drug into the lateral tail vein. The mean maximum percent effect (% MPE) was calculated for each time period, and a time effect curve was generated. We have defined a test compound to be short acting if the duration to 50% MPE was less than 6 min, intermediate with a duration of 6.1–15 min, and long acting with a duration greater than 15.1 min.

Loss of Righting[12] (LOR). Male Swiss-Webster mice weighing 18–26 g with free access to food and water were marked, weighed, and allowed to acclimate for 1 h in the laboratory environment.

The starting dose was usually 15.5 mg/kg with use of three mice per dose. The range of doses tested was that dose that elicits death in 1/3 mice (lowest lethal dose LLD) decreasing to a dose that does not produce loss of righting (LOR) in 0/3 mice.

Immediately following a bolus injection into one of the lateral tail veins, a stopwatch was started and the mouse was placed on his dorsal side. Failure to return to the ventral side indicates LOR. Duration of LOR was recorded as the time from LOR until righting occurred. The lowest dose required to produce loss of righting in 3/3 mice (lowest effective dose 100, LED_{100}) was used as a standard for comparing the test compounds.

Opiate Receptor Binding. The method was based on that of Pasternak[13] et al. and used crude membrane fractions prepared from freshly harvested rat brains. Doses of 1, 10, and 100 nM were run in triplicate, and the data curve was fitted to the mean. The K_i for inhibition of [^{3}H]nalaxone binding was then calculated according to the method of Cheng and Prusoff.[14]

Acknowledgment. The technical assistance of Mark Benvenga, Thomas Jerrussi, Steve Waters, and Barry I. Gold (Anaquest Pharmacology Department, Murray Hill, NJ) and of the Dental School of the University of Maryland at Baltimore is gratefully acknowledged. We also thank the discussions and valuable insight of Dr. Jerome R. Bagley (Anaquest Chemistry Department) during the course of this investigation.

Supplementary Material Available: A listing of the NMR data for **1–5** (4 pages). Ordering information is given on any current masthead page.

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9,11-Epoxy-9-homo-14-thiaprost-5-enoic Acid Derivatives: Potent Thromboxane A_2 Antagonists

Steven E. Hall,* Wen-Ching Han, Don N. Harris, Anders Hedberg, and Martin L. Ogletree

Departments of Chemistry and Pharmacology, Squibb Institute for Medical Research, P.O. Box 4000, Princeton, New Jersey 08543-4000. *Received December 21, 1987*

A novel bicyclic prostaglandin analogue, (1*S*)-[1α,2α(*Z*),3α,4α]-7-[3-[(hexylthio)methyl]-7-oxabicyclo[2.2.1]hept-2-yl]-5-heptenoic acid ((−)-**10**), and its cogeners were found to be potent antagonists at the TxA_2 receptor. Compound (−)-**10** was the only stereoisomer out of eight possible structures that was active. Thioether (−)-**10** was 30–40-fold more potent than another TxA_2 antagonist, BM 13.177, in inhibiting arachidonic acid (AA) induced aggregation of human platelet-rich plasma. Compound (−)-**10** was effective (I_{50} = 0.5 ± 0.4 μM) in inhibiting 9,11-azo-PGH_2-induced (0.1 μg/mL) contraction of guinea pig tracheal spirals. The bronchoconstriction in anesthetized guinea pigs induced by AA was also effectively antagonized by (−)-**10** (1 mg/kg, iv); however, in this assay (−)-**10** exhibited some direct agonist activity. Radioligand binding studies in washed (human) platelets revealed that (−)-**10** is one of the most potent ligands for the PGH_2/TxA_2 receptor yet described (K_d = 1.6 ± 0.4 nM).

The development of pharmacological agents that modulate the synthesis or actions of a variety of arachidonic acid (AA) metabolites continues to be an active area of research. Our interest in the AA manifold has focused on the least stable member of this family, namely thromboxane A_2 (TxA_2, **1**).[1] This compound, whose structural

0022-2623/89/1832-0974$01.50/0