37926-90-2; **42**, 2240-28-0; **43**, 5534-12-3; **44**, 23640-98-4; **45**, 29379-85-9; **46**, 23640-97-3; **47**, 23641-10-3; **48**, 124-94-7; **49**, 1177-87-3; **50**, 37792-94-2; **51**, 15180-00-4; **52**, 37926-92-4; **53**, 2693-06-3; **54**, 4419-39-0; **55**, 1597-82-6; **56**, 23641-05-6; **57**, 25122-48-9; **58**, 302-25-0; **59**, 37926-95-7; **60**, 37927-21-2; **61**, 37926-89-9; **62**, 5534-14-5; **63**, 75883-07-7; **64**, 57524-89-7; **65**, 103836-56-2; **66**, 638-94-8; **67**, 514-36-3; **68**, 83-43-2; **69**, 84099-87-6; **70**, 52510-28-8; **71**, 25092-07-3; **72**, 84099-88-7; **73**, 37927-23-4; **74**, 23641-03-4; **75**, 37792-93-1; **76**, 23674-85-3; **77**, 806-29-1; **78**, 37792-98-6; **79**, 37926-93-5; **80**, 382-67-2; **81**, 641-77-0; **82**, 5593-20-4; **83**, 37926-96-8; **84**, 4351-48-8; **85**, 23641-04-5; **86**, 37872-65-4; **87**, 103836-58-4; **88**, 29379-86-0; **89**, 23640-96-2; **90**, 42363-29-1; **91**, 53-34-9; **92**, 28971-62-2; **93**, 2802-11-1; **94**, 37926-76-4; **95**, 84099-92-3; **96**, 749-69-9; **97**, 23674-86-4; **98**, 25450-34-4; **99**, 16463-74-4; **100**, 2668-66-8; **101**, 82034-75-1; **102**, 5534-13-4; **103**, 3863-59-0; **104**, 84099-93-4; **105**, 23641-07-8; **106**, 84099-94-5; **107**, 807-38-5; **108**, 23641-01-2; **109**, 630-44-4; **110**, 25122-41-2; **111**, 23641-09-0; **112**, 23641-02-3; **113**, 5534-18-9; **114**, 42363-32-6; **116**, 103851-06-5; **117**, 72064-79-0; **118**, 23641-08-9; **119**, 37792-97-5; **120**, 360-63-4; **121**, 61774-17-2; **122**, 25122-45-6; **123**, 23641-10-3.

Probes for Narcotic Receptor Mediated Phenomena. 13.[1] Potential Irreversible Narcotic Antagonist-Based Ligands Derived from 6,14-*endo*-Ethenotetrahydrooripavine with 7-(Methoxyfumaroyl)amino, (Bromoacetyl)amino, or Isothiocyanate Electrophiles: Chemistry, Biochemistry, and Pharmacology

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N-Allyl-, *N*-(cyclopropylmethyl)-, and *N*-propyl-*endo*-ethenotetrahydronororipavines (N-substituted 6,14-*endo*-etheno-4,5-epoxy-3-hydroxy-6-methoxymorphinans) were synthesized with potential acylating or alkylating moieties at the C-7 position (isothiocyanato, (bromoacetyl)amino, and (methoxyfumaroyl)amino) and examined in vivo for their narcotic agonist and antagonist activities and for their ability to interact with opioid receptors in vitro. The *N*-(cyclopropylmethyl)-substituted compounds were found to have the highest affinity for opioid receptors among these N-substituted compounds, although all of them were found to be reasonably potent narcotic antagonists in the mouse tail flick vs. morphine assay. Their in vivo potency ranged from $^1/_8$ to 4 times that of nalorphine on intravenous injection in mice. Rat brain membrane binding studies indicated that the compounds interacted with opioid receptors with potencies that ranged from 0.5 times that of morphine (**8c**, **9c**, and **10c**) to 0.017 that of morphine (**8b**). Among the compounds studied here, only the previously reported isothiocyanato compound (**10c**) and (methoxyfumaroyl)amino compound (**8c**) interacted irreversibly and selectively with μ or δ opioid receptors, respectively, in assays using NG108-15 neuroblastoma–glioma hybrid cells and/or in a rat brain membrane preparation. Both **8c** and **10c** were found to interact irreversibly, to a limited extent, with κ opioid sites in rat brain membranes in which the μ and δ opioid receptors were depleted by interaction with the μ-selective irreversible ligand BIT and the δ-selective irreversible ligand FIT. Neither compound showed irreversible actions in the electrically stimulated mouse vas deferens preparation.

Irreversible ligands[2] for specific opioid receptors[3] are valuable tools for a number of purposes. For example, we have previously reported the characterization of a covalently labeled glycopeptide subunit of the δ opioid receptor using FIT, an opioid agonist which specifically acylates this receptor class.[4a] Using a more potent acylating analogue, we have now purified this subunit to apparent homogeneity.[4b] Specific covalent modifying agents can also be utilized for the production of antibodies to drugs, and these can lead to antiidiotypic antibodies to the receptor.[5] Affinity columns for purification of receptors can be prepared with these selective modifying agents.[6] Autoradiographic mapping of receptor subtypes in brain sections[7] and the determination of the effect of receptor occupancy in individual neurons using electrophysiological techniques[8] can also be carried out using specific affinity ligands. For these reasons, we have been engaged in a program to identify a number of different affinity ligands that would be specific for each of the known, or purported, types of opioid receptors.

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[‡] Deceased June 7, 1983.
[§] National Institute of Mental Health.
[⊥] The University of Michigan.
[∥] Virginia Commonwealth University.

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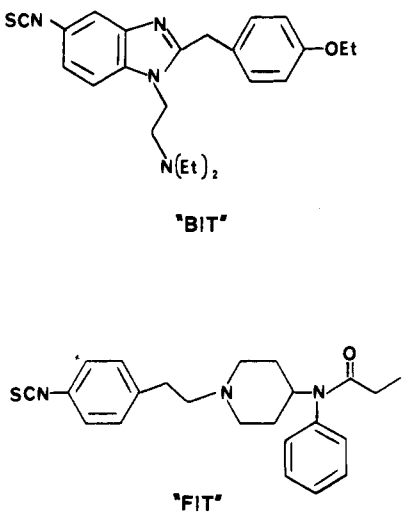
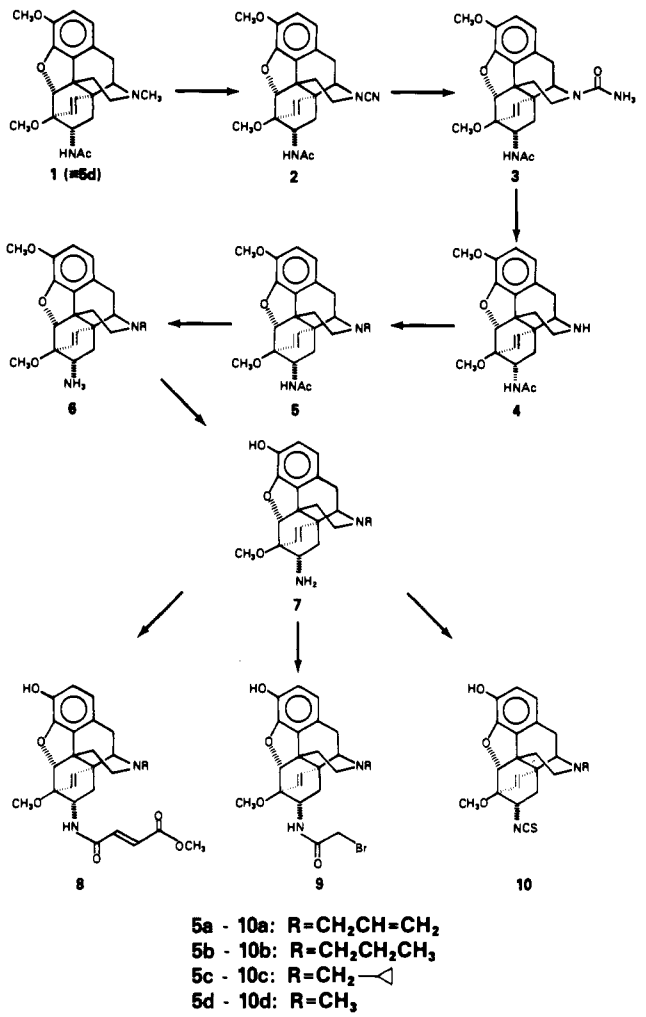


Figure 1. Structures of BIT and FIT.

We have previously reported the synthesis and pharmacological and biochemical properties of three affinity ligands, FIT (*N*-[1-[2-(4-isothiocyanatophenyl)ethyl]-4-piperidinyl]-*N*-phenylpropanamide), BIT (1-[2-(diethylamino)ethyl]-2-(4-ethoxybenzyl)-5-isothiocyanatobenzimidazole) (Figure 1), and FAO (*N*-methyl-6,14-*endo*-etheno-7α-[(methoxyfumaroyl)amino]tetrahydronororipavine, **8d**) (Scheme I), which specifically interacted with either μ or δ opioid receptors.[9,10] The latter compound, FAO, was based on the 6,14-*endo*-ethenotetrahydrooripavine class of compounds. It seemed likely that the usual method for conversion of narcotic analgesics to their antagonists, the replacement of the *N*-methyl group by an *N*-allyl, *N*-(cyclopropylmethyl), or *N*-propyl moiety, could produce specific affinity ligands for opioid receptors that were narcotic antagonists. Thus, we have synthesized the *N*-allyl-, *N*-(cyclopropylmethyl)-, and *N*-propyl-6,14-*endo*-ethenotetrahydrooripavines, with the acylating or alkylating moieties (isothiocyanato, (bromoacetyl)amino, and (methoxyfumaroyl)amino) at the C-7 position. We have reported our initial biochemical results with a few of these narcotic antagonists,[11] one of them (**10c**), with an isothiocyanato moiety at C-7, being a selective acylating agent for μ opioid receptors. The isothiocyanato moiety has been found to be very effective at acylating opioid[9,10] and other CNS receptors.[12,13] A second compound (**8c**), with a (methoxyfumaroyl)amino moiety,[14] was found to be a selective irreversible ligand for δ opioid receptors. It was considerably more potent (ca. 10-fold higher affinity) than FAO. This was the first example of an electrophilic affinity ligand that appeared to be specific for δ opioid receptors in the narcotic antagonist series. We now wish to render a full account of the synthesis, pharmacological, and biochemical properties of these and other potential affinity ligands bearing the N side chains theoretically appropriate for producing narcotic antagonists.

Scheme I



Chemistry. All compounds were prepared from the known 7α-(acetylamino)-6,14-*endo*-ethenotetrahydrothebaine (**1**).[15] The key transformation in the preparation of the *N*-alkyl-6,14-*endo*-ethenotetrahydrooripavine derivatives was the selective hydrolysis of the *N*-cyano protecting group in diprotected compound **2**. Compound **2** was prepared from **1** by cyanogen bromide mediated N-demethylation.[16] Mild acidic hydrolysis of **2** afforded urea **3** without disturbing the *N*-acetyl protecting group. The urea **3** was converted smoothly into nor compound **4** by nitrite-promoted hydrolysis and subsequent decarboxylation.[17] This selective hydrolysis scheme allowed exclusive alkylation of the secondary amine of **4** with the appropriate

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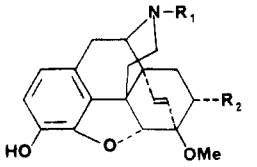
Table I. Biochemical and Biological Evaluation



compd no.	R_1	R_2[a]	binding EC_{50},[b] nM, rat brain	% irrev inhibn of rat brain κ sites (no. expts)	ED_{50},[c] mg/kg hot plate, sc	ED_{50},[c] mg/kg TF vs. morphine, iv
8a oxalate	allyl	MF	90	1 (1)	inactive[d]	6.3 (5.1–7.8)
9a oxalate	allyl	BA	90	1 (1)	inactive	2.1 (0.8–5.7)
10a oxalate	allyl	NCS	100	12 (1)	inactive	0.6 (0.3–1.1)
7a oxalate	allyl	NH_2	50		7.6 (5.0–11.6)	
8b base[e]	propyl	MF	180	1 (1)	inactive	1.8 (0.9–3.6)
9b base	propyl	BA	130	5 (1)	inactive	0.6 (0.3–1.2)
10b oxalate	propyl	NCS	130	16 (1)	inactive	0.7 (0.3–1.5)
7b oxalate	propyl	NH_2	100		inactive	inactive[f]
8c oxalate	CPM[g]	MF	6	20 (1)	inactive	1.5 (0.6–3.8)
9c base	CPM	BA	7	13 (4)	inactive	0.4 (0.2–0.9)
10c oxalate	CPM	NCS	7	40 (4)	inactive	0.2 (0.1–0.4)
7c base	CPM	NH_2	6		inactive	ca. 30[h]
nalorphine hydrochloride			1.5		9.9 (5.7–17.1)	0.8 (0.3–2.0)
morphine sulfate			3		1.3 (0.9–1.6)	

[a] Key: MF, (methylfumaryl)amino; BA, (bromoacetyl)amino; NCS, isothiocyanato. [b] The EC_{50} values are based on two or more determinations and are considered reliable within a factor of 2. [c] In mice; 95% confidence limits shown in parentheses, as obtained through computerized probit analysis. [d] Inactive compounds were tested at 2 and 20 mg/kg. [e] The bases were dissolved by addition of 1.0 equiv of aqueous HCl and further diluted; the salts were dissolved in water. [f] Inactive at 0.1, 1, and 10 mg/kg. [g] Key: CPM, cyclopropylmethyl. [h] Of the mice 52% were effected at 30 mg/kg, 30% at 10 mg/kg, and 5% at 3 mg/kg.

alkyl halide to give the 7α-(acetylamino)-*N*-alkyl-6,14-*endo*-ethenotetrahydronorthebaines **5a–c**.

Hydrolysis of the *N*-acetyl protecting group of compounds **5a–c** was achieved by treatment with 3 N hydrochloric acid at 110 °C to give the *N*-alkyl-7α-amino-6,14-*endo*-ethenotetrahydronorthebaines **6a–c**. Boron tribromide mediated O-demethylation of the phenolic ether[18] proceeded smoothly to give the corresponding *N*-alkyl-7α-amino-6,14-*endo*-ethenotetrahydronororipavines **7a–c**.

The 7α-amino group of compounds **7a–c** was then converted into a suitable electrophilic functionality for possible receptor labeling. The corresponding *N*-methoxyfumaroyl[14] derivatives **8a–c** were prepared by reaction with methoxyfumaroyl chloride[19] in a two-phase system consisting of chloroform and aqueous sodium bicarbonate. The bromoacetamides **9a–c** were prepared in a similar manner by condensation with bromoacetyl chloride. The isothiocyanates **10a–c** were prepared by condensation of the amino compounds **7a–c** with redistilled thiophosgene[9] in the same two-phase system employed for condensation with the acid chlorides. The synthesis and characterization of the *N*-methyl analogues have been detailed elsewhere.[9] All potential affinity labels were converted into suitable water-soluble salts for biological evaluation.

Biology. The binding affinities of the various compounds for the opioid receptors in the rat brain membrane preparation were determined by displacement of [^{3}H]dalamid ([D-Ala^2,Met^5]enkephalinamide). Their binding affinity ranged from those which were essentially morphine-like (**7c**, **8c**, **9c**, and **10c**) to those which had considerably lower affinity than morphine or nalorphine (Table I). The interactions of the *N*-(cyclopropylmethyl) compounds **8c**, **9c**, and **10c** with μ and δ opioid receptor populations have been described.[11]

Brain membranes treated with BIT and FIT to remove the μ and δ opioid receptor populations still bound [^{3}H]-EKC (ethylketocyclazocine) at what we presume to be the κ sites. At the 100 nM concentration used for the incubation, BIT effectively removed all of the μ sites. Under the conditions of the experiment, we found that etonitazene, a potent μ agonist,[10] could no longer displace [^{3}H]dalamid from the rat brain membrane preparation. With the use of such preparations it has been found that only a few of the antagonist ligands could irreversibly block the remaining (κ) sites (see Table I). The most potent affinity ligand for the κ sites was **10c**. It irreversibly blocked about 40% of the κ sites under the conditions of the experiment.

Both **10c**[11] and **8c** were found to have narcotic antagonist properties in an adenylate cyclase assay using NG108-15 cells (which indicates the agonist vs. antagonist properties of the molecule).[20] These compounds, as well as the others (Table I) were tested in vivo in the tail flick antagonist assay vs. morphine, and the hot plate assay, as indicators of the antagonist and/or agonist nature of the compounds in vivo. It should be noted, however, that in vivo data from acylating agents introduced intravenously or subcutaneously may not be indicative of the effects of the compound itself, but rather of some product derived from it, perhaps by reaction of the electrophilic function during transport from the periphery to the CNS. Since these in vivo assays do not discriminate between reversible and irreversible actions, it cannot be conclusively stated that the test compound arrives intact at its site of action. The *N*-methyl compounds **8d**, **9d**, and **10d** that had acylating moieties at C-7 showed opioid agonist activities and were morphine-like in potency;[9] none of the potential affinity ligands with antagonist side chains had detectable agonist activity in the hot plate assay (sc, in mice). Among the compounds with a free amino group at C-7 (**7a–d**), only the *N*-allyl compound (**7a**) displayed detectable agonist activity in this assay (ca. 0.16 that of morphine).

The C7-amino compounds **7a–c** displayed little, if any, narcotic antagonist activity in the tail flick vs. morphine assay (iv, in mice). However, all of the potential affinity

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ligands with antagonist-type side chains on nitrogen (**8a–c**, **9a–c**, **10a–c**) displayed narcotic antagonist activity in this assay. Their potency ranged from 4 times that of nalorphine (**10c**) to $^1/_8$ that of nalorphine (**8a**). It is of interest to note that compound **8c** had a relatively long duration of action in vivo. After 3 h, 82% (±13%) of its antagonist activity was retained against an ED_{80} dose of morphine (9 mg/kg). Even after 6 h, 26% (±5%) of the antagonist activity was found. Normally, little or no antagonist activity is found ca. 2 h after iv introduction of naloxone or sc introduction of naloxone or naltrexone in the tail flick antagonism test in mice.[21] In view of the failure of **8c** to acylate μ receptors in vitro, its prolonged action as an antagonist in this assay (which, presumably, is indicative of μ effects) is somewhat surprising.

In the electrically stimulated mouse vas deferens preparation, the δ receptor agonist DSLET (Tyr-D-Ser-Gly-Phe-Leu-Thr) was a very potent inhibitor of the twitch. The EC_{50} of this opioid was 33.2 ± 1.1 nM, and the maximum effect was a complete inhibition of the twitch (n = 12). Both **10c** and **8c** at a concentration of 100 nM caused parallel shifts to the right in the DSLET concentration–effect curve. In the presence of **10c**, the EC_{50} for DSLET was 148.8 ± 1.56 nM (n = 4). In the presence of **8c**, the EC_{50} for DSLET was 740.0 ± 15.6 nM (n = 5). DSLET caused a complete inhibition of the twitch in the presence of both antagonists. Alfentanil, a highly selective μ receptor agonist, was approximately equipotent with morphine as an inhibitor of the twitch of vas deferens preparation. The EC_{50} for alfentanil in control experiments was 111.6 ± 2.73 nM, and the maximum response was an 89.9% (±3.9%) inhibition of the twitch. Both **10c** and **8c** in a 100 nM concentration shifted the concentration–effect curve for alfentanil to the right and decreased the maximum response. In the presence of **10c**, the EC_{50} for alfentanil was 3.53 ± 0.91 μM, and the maximum response was a 51.2% (±1.4%) inhibition of the twitch (n = 5). In the presence of **8c**, the EC_{50} for alfentanil was 2.50 ± 0.36 μM, and the maximum response was a 58.7% (±1.7%) inhibition (n = 3). In some experiments vasa deferentia were incubated for 30 min with either **10c** or **8c** and then washed repeatedly for an additional 25 min with fresh buffer. In these experiments neither antagonist (**10c** or **8c**) shifted the concentration–effect curves for either DSLET or alfentanil, which indicates that both are reversible under these conditions in this system.

Discussion and Conclusion

The specificity of affinity ligands derived from opioid-type drugs is difficult to predict on the basis of molecular structure. FIT, an acylating ligand based on the μ-selective agonist fentanyl, has shown selectivity for δ receptors in its irreversible interactions, while BIT, based on μ-selective etonitazine, is μ selective. Nor is selectivity dependent on the type of reactive group present, since, for example, both μ- and δ-selective isothiocyanate ligands have been demonstrated.[10] We have demonstrated that in the *endo*-ethenotetrahydrooripavine series, the agonist or antagonist nature of the nitrogen side chain does not determine μ–δ selectivity.

It seems logical to suppose that the selectivity of these compounds might be related to the spatial location of the electrophilic moiety relative to the various features of the molecule responsible for reversible binding to opioid receptors. The cyclopropylmethyl isothiocyanate **10c** is a μ-selective irreversible opioid receptor ligand.[11] If spatial location of the reactive group is the primary basis for receptor type discrimination, one would predict that the corresponding *N*-methyl (agonist-based) isothiocyanate compound **10d** would also display selectivity for μ opioid receptors in any irreversible interaction. In accord with this prediction, we have found that **10d** does selectively acylate the μ opioid receptor without interacting irreversibly with δ receptors, but it does so only at high concentrations (200 nM) and to only a limited extent (50% of the μ receptors in rat brain membranes were inactivated at the 200 nM concentration). It should be noted in passing that the corresponding *N*-allyl (**8a** and **10a**) and *N*-propyl (**8b** and **10b**) compounds did not show sufficient receptor affinities in displacement assays vs. [^{3}H]dalamid to warrant testing as μ or δ irreversible ligands.

By elimination of both the δ and μ opioid receptor populations in the P2 fraction by pretreatment with FIT and BIT, respectively, we can now test compounds against the remaining population of receptors. BIT and FIT have previously been utilized to completely inactivate the μ and δ opioid receptors in rat brain membranes for autoradiographic studies.[7b] In that study, residual κ opioid receptors were visualized by using [^{3}H]bremazocine. As noted in Table I, **8c** irreversibly interacted with 20% of the κ sites and **10c** with 40% of those sites at a concentration of 100 nM, thus indicating that, while these compounds may discriminate between μ and δ receptors in their irreversible interactions, their specificity is not absolute.

In the mouse vas deferens preparation, the highly selective δ receptor antagonist ICI-174,864 [*N*,*N*-diallyl-Tyr-Aib-Aib-Phe-Leu-OH] in low concentrations markedly shifts the concentration–effect curve for DSLET to the right, but does not alter responses to μ receptor agonists such as alfentanil even in high concentrations.[22,23] In the present study, both **10c** and **8c** in a concentration of 100 nM caused shifts to the right in the concentration–effect curves for both the μ receptor agonist alfentanil and the δ receptor agonist DSLET. Compound **10c** caused larger shifts than did **8c** in the curves for both agonists. Thus, in the mouse vas deferens preparation the effects of **10c** and **8c** are surmountable, and neither shows the high degree of selectivity for either the μ or the δ receptor such as that seen with ICI-174864 for the δ receptor. The failure of these compounds to act irreversibly in the mouse vas deferens preparation, while they were clearly acting irreversibly on receptors in brain membrane preparations,[11] may be indicative of subtle differences between the receptors in these organs.

In conclusion, the *N*-(cyclopropylmethyl) compounds **8c**, **9c**, and **10c** were narcotic antagonists in vivo and in vitro and had the highest affinity for opioid receptors of any of the N-substituted compounds examined. These ligands show narcotic antagonist activity in the tail flick antagonism assay, in which they may interact with μ receptors, and **8c** and **10c** also show narcotic antagonist activity in the adenylate cyclase assay in NG108-15 cells, where they certainly interact with δ opioid receptors. It is likely that these compounds, like FIT,[24] can reversibly interact with either μ or δ receptors, although they have been shown to be μ (**10c**) or δ selective (**8c**) in their irreversible interac-

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tions.[11] Both affinity ligands **8c** and **10c** have now been shown to have some irreversible actions on the κ site in rat brain membrane preparations depleted of μ and δ opioid receptors (Table I), and neither displayed selectivity or irreversible interaction with the μ/δ receptor population in the electrically stimulated mouse vas deferens preparation. Compound **8c** was found to have a considerably longer duration of action in vivo (tail flick antagonism assay, iv introduction) than naloxone.

Experimental Section

Biological Methods. In Vitro. Cell lines, assay of adenylate cyclase of intact cells, and binding to NG108-15 cells have been described previously;[20] the determination of opiate receptors remaining in NG108-15 cell membranes, incubation techniques, and the method for displacement of labeled ligands from rat brain membranes by etonitazene have also been described.[10]

κ Site Experiments. Frozen rat brain P_2 preparations,[25] 2 mg of protein/mL, were thawed, diluted with 2 vol of 10 mM potassium phosphate buffer, pH 8.0, and centrifuged at 40 000 rpm for 30 min. The membranes were resuspended in 1.5 vol (compared to the original volume) of phosphate buffer and incubated for 30 min at 37 °C with 10^{-7} M FIT, BIT, and the compound being tested. At the end of the incubation, the membranes were diluted with 6 vol of 10 mM Tris-HCl, pH 7.8, and centrifuged at 40 000 rpm for 30 min. The pellets were resuspended in 7 vol of Tris, centrifuged as before, and finally resuspended in the original volume of 10 mM Tris-HCl, pH 7.8. Binding of 10 μM [^{3}H]EKC was measured in 500-μL aliquots of this suspension as described previously.[26] Nonspecific binding was defined as radioactivity remaining associated with the membranes in the presence of 10^{-5} M diprenorphine. All assays were in triplicate.

In Vivo. Tail Flick vs. Morphine Assay. The procedure[27] and modifications[28] have been described. Briefly, the mouse's tail was placed in a groove that contained a slit under which was located a photoelectric cell. When the heat source or noxious stimulus was turned on, it focused on the tail and the animal responded by flicking its tail out of the groove. Thus, light passed through the slit and activated the photocell, which in turn stopped the recording timer. The heat source was adjusted to produced tail flick latencies of 2–4 s under control conditions. Swiss–Webster ICR mice were injected in a tail vein with the antagonists 10 min before the subcutaneous injection of an EC_{80} dose of morphine and tested 20 min later. For each drug, at least three doses were tested and six animals per dose were used.

Electrically Stimulated Mouse Vas Deferens Assay. Male, albino ICR mice, weighing between 25 and 30 g, were used. The mice were sacrificed by decapitation, the vasa deferentia removed, and 1.5-cm segments suspended in organ baths that contained 30 mL of a modified Krebs' physiological buffer. The buffer contained the following (mM): NaCl, 118; KCl, 4.75; $CaCl_2$, 2.54; $MgSO_4$, 1.19; KH_2PO_4, 1.19; glucose, 11; $NaHCO_3$, 25; pargyline hydrochloride, 0.3; tyrosine, 0.2; ascorbic acid, 0.1; and disodium edetate, 0.03. The buffer was saturated with 95:5 O_2–CO_2 and kept at 37 °C. The segments were attached to strain gauge transducers and suspended between two platinum electrodes. After a 30-min equilibration period, the segments were stimulated once every 10 s with pairs of pulses of 2-ms duration, 1 ms apart, and at a supramaximal voltage. The antagonists were added in a concentration of 100 nM 15 min before the determination of cumulative concentration–effect relationships for alfentanil, a selective μ receptor agonist, or for DSLET [Tyr-D-Ser-Gly-Phe-Leu-Thr], a selective δ receptor agonist. EC_{50}'s were calculated by probit analysis. All values are reported as the means of n determinations ± the standard error of the mean.

Synthesis. Melting points were determined on a Thomas-Hoover capillary apparatus and are corrected. NMR spectra were recorded with a Varian 220-MHz spectrometer. Electron ionization mass spectra (EIMS) were obtained with a Hitachi Perkin-Elmer RMU-6E spectrometer (70 eV). Chemical ionization mass spectra (CIMS) were obtained with a Finnigan 1015D spectrometer with a Model 6000 data collection system. Column chromatography was performed by use of 230–400-mesh EM silica gel. Flash chromatography was performed on a mixture of Merck 7736 and 9385 silica gels (10:1). Thin-layer chromatography was performed on Analtech silica gel plates.

7α-(Acetylamino)-6,14-*endo*-ethenonorthebaine (4). A solution of **1**[15] (18.4 g, 46 mmol) and cyanogen bromide (11.0 g, 103 mmol) in alcohol-free $CHCl_3$ (150 mL) was heated at reflux. After 16 h, additional cyanogen bromide (1.0 g) was added, and reflux was continued for an additional 4 h. The mixture was cooled to room temperature, and solvent was removed in vacuo to give **2** as a white foam.

The crude **2** was added to 1 N HCl (500 mL) and heated to 90 °C. The reaction was monitored by TLC using 95:5:1 $CHCl_3$–MeOH–concentrated NH_4OH. Upon complete disappearance of starting material, the mixture was cooled to room temperature and extracted with $CHCl_3$ (4 × 150 mL). The combined organics were dried ($MgSO_4$) and evaporated in vacuo to give **3** as a white foam (19.1 g).

The residual foam **3** was added to 1 N HCl (800 mL) and cooled to 0 °C, treated with a solution of $NaNO_2$ (5.5 g, 80 mmol) in water (30 mL) added in small portions, and then stirred for 4 h at 0 °C. The mixture was made basic with 10% aqueous NaOH solution and extracted with $CHCl_3$ (4 × 300 mL). The combined organics were dried (Na_2SO_4) and evaporated in vacuo. Addition of acetone induced crystallization. Filtration afforded **4** as a white solid (8.9 g, 50% from **1**): mp 255–256 °C; EIMS, m/e 382 (M^+), 297. Anal. ($C_{22}H_{26}N_2O_4$) C, H, N.

7α-(Acetylamino)-*N*-allyl-6,14-*endo*-ethenotetrahydronorthebaine (5a). A solution of **4** (3.82 g, 10 mmol) in EtOH (200 mL) was treated with anhydrous Na_2CO_3 (5.0 g, 47 mmol) and allyl bromide (1.21 g, 10 mmol). The mixture was heated at reflux for 16 h, cooled to room temperature, and filtered. Solvent was removed in vacuo, and the residue was dissolved in $CHCl_3$ (200 mL) and washed with H_2O (200 mL). The organic layer was dried (Na_2SO_4) and evaporated. The residue was dissolved in hot aqueous methanol and cooled, affording **5a** as colorless prisms (3.45 g, 82%): mp 100–101 °C: CIMS (CH_4), m/e 423 ($M + H^+$). Anal. ($C_{25}H_{30}N_2O_4 \cdot 0.25CH_3OH$) C, H, N.

7α-(Acetylamino)-6,14-*endo*-etheno-*N*-propyltetrahydronorthebaine (5b). A solution of **4** (3.0 g, 7.85 mmol) in ethanol (200 mL) was treated with anhydrous Na_2CO_3 (5.0 g, 47 mmol) and 1-bromopropane (1.26 g, 10.2 mmol). The mixture was heated at reflux for 30 h, then cooled, filtered, and evaporated. The residue was dissolved in $CHCl_3$ (100 mL) and washed with H_2O (50 mL). The organic layer was dried (Na_2SO_4) and evaporated to an oil, which crystallized from Et_2O/petroleum ether to give **5b** as colorless prisms (2.85 g, 85%): mp 92–93 °C: CIMS (NH_3), 425 ($M + H^+$). Anal. ($C_{25}H_{32}N_2O_4 \cdot 0.25H_2O$) C, H, N.

7α-(Acetylamino)-*N*-(cyclopropylmethyl)-6,14-*endo*-ethenotetrahydronorthebaine (5c) Oxalate. A mixture of **4** (4.42 g, 11.6 mmol), sodium bicarbonate (3.0 g, 35.7 mmol), (cyclopropylmethyl bromide (1.61 g, 11.9 mmol), and DMF (50 mL) was heated at 85 °C for 4 h, then cooled to room temperature and evaporated in vacuo. The residue was partitioned between $CHCl_3$ (50 mL) and H_2O (50 mL). The organic layer was separated, dried ($MgSO_4$), and evaporated in vacuo. The residual clear oil was dissolved in acetone (10 mL) and treated with 1.1 equiv of a saturated solution of oxalic acid in acetone, heated to boiling, and diluted with isopropyl ether to the cloud point, then allowed to cool slowly. After overnight storage at −5 °C, the resulting crystals were collected, washed with isopropyl ether, and dried. Concentration of the mother liquor and seeding afforded a second crop of the oxalate, total yield 4.51 g (74%). The salt was recrystallized from acetone/isopropyl ether to give **5c** oxalate: mp 227–228 °C dec; EIMS, m/e 436 (M^+), 351. Anal. ($C_{26}H_{32}N_2O_4 \cdot C_2H_2O_4$) C, H, N.

***N*-Alkyl-7α-amino-6,14-*endo*-ethenotetrahydronorthebaines (6a–c). General Procedure.** A solution of the appropriate compound **5** in 3 N HCl was heated at 110–115 °C until TLC (95:5:1 $CHCl_3$–MeOH–concentrated NH_4OH) indicated that hydrolysis was complete. The reaction mixture was cooled,

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rendered basic to pH 10 with concentrated NH_4OH, and extracted three times with $CHCl_3$. The organics were dried (Na_2SO_4) and evaporated to give the product as an oil.

6a Dioxalate: Crystallized from acetone (88%); mp 184–185 °C dec; CIMS (NH_3), m/e 381 ($M + H^+$). Anal. ($C_{23}H_{28}N_2O_3 \cdot 2C_2H_2O_4 \cdot 1.5H_2O$) C, H, N.

6b Dioxalate: Crystallized from acetone (93%); mp 171–172 °C dec; CIMS (NH_3), m/e 383 ($M + H^+$). Anal. ($C_{23}H_{30}N_2O_3 \cdot 2C_2H_2O_4 \cdot 1.5H_2O$) C, H, N.

6c Oxalate: Crystallized from acetone (94%); mp 105–115 °C (loss of water), 160 °C dec; EIMS, m/e 394 (M^+), 379, 351, 255. Anal. ($C_{24}H_{30}N_2O_3 \cdot C_2H_2O_4 \cdot H_2O$) C, H, N.

***N*-Alkyl-7α-amino-6,14-*endo*-ethenotetrahydronororipavines (7a–c). General Procedure.** A 10% w/v solution of the appropriate compound **6** in $CHCl_3$ was added dropwise to a well-stirred 25% v/v solution of BBr_3 (10 mol equiv) in $CHCl_3$ that had been precooled to 0–5 °C. The mixture was stirred and allowed to warm to room temperature. After 30 min, the reaction was poured onto a mixture of ice and concentrated NH_4OH and stirred for 15 min. The phases were separated, and the aqueous layer was washed with $CHCl_3$. The combined organics were dried (Na_2SO_4) and evaporated. The residual oil was purified by flash chromatography on silica gel using methylene chloride–methanol–concentrated NH_4OH (96:3:1) as the eluting solvent.

7a: Crystallized from acetone as colorless prisms (67%); mp 112–113 °C; CIMS (NH_3), m/e 367 ($M + H^+$). Anal. ($C_{22}H_{26}N_2O_3 \cdot 0.5H_2O$) C, H, N.

7b: Crystallized from acetone as colorless prisms (64%); mp 110–111 °C; CIMS (NH_3), 369 ($M + H^+$). Dioxalate Salt: Crystallized from acetone; mp 181–183 °C. Anal. ($C_{22}H_{28}N_2O_3 \cdot 2C_2H_2O_4 \cdot H_2O$) C, H, N.

7c: Crystallized from petroleum ether as colorless prisms; mp 115–116 °C. Optimal yield (96%) could be achieved by conversion of crude product to the oxalate salt in isopropyl alcohol; mp 172–175 °C dec. Recrystallization from wet methanol afforded analytically pure material: mp 174–175 °C dec; EIMS, m/e 380 (M^+). Anal. ($C_{23}H_{28}N_2O_3 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

***N*-Alkyl-6,14-*endo*-etheno-7α-[(methoxyfumaroyl)amino]tetrahydronororipavines (8a–c). General Procedure.** To a rapidly stirred mixture of the appropriate compound **7** (250 mg), $NaHCO_3$ (5 equiv), $CHCl_3$ (15 mL), and water (10 mL) was added methoxyfumaroyl chloride[19] (1.1 equiv). The mixture was stirred vigorously for 20 min, and then the phases were separated. The organic phase and washed with 1 N NH_4OH, then with water. The organic phase was dried (Na_2SO_4) and evaporated. The product was purified by flash chromatography on silica gel using 90:9:1 $CHCl_3$–MeOH–concentrated NH_4OH as the eluting solvent.

8a: Crystallized from petroleum ether (70%); mp 128–129 °C. Oxalate Salt: Prepared and crystallized from acetone; mp 185–188 °C dec; CIMS (NH_3), m/e 479 ($M + H^+$). Anal. ($C_{27}H_{30}N_2O_6 \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N.

8b: Crystallized from petroleum ether (72%); mp 123–124 °C; CIMS (NH_3), m/e 481. Anal. ($C_{27}H_{32}N_2O_6 \cdot 0.5H_2O$) C, H, N. Oxalate: Crystallized from acetone; mp 163–164 °C dec.

8c: Crystallized from petroleum ether (76%); mp 119–120 °C; CIMS (NH_3), m/e 493 ($M + H^+$). Anal. ($C_{28}H_{32}N_2O_6 \cdot H_2O$) C, H, N. Oxalate: Crystallized from acetone/ether; mp 165–167 °C dec.

***N*-Alkyl-7α-(bromoacetyl)amino-6,14-*endo*-ethenotetrahydronororipavines (9a–c). General Procedure.** A mixture of the appropriate compound **7** (1 mmol), $NaHCO_3$ (5 equiv), $CHCl_3$ (15 mL), and water (10 mL) was stirred vigorously and treated with a solution of bromoacetyl chloride (1.1 equiv) in $CHCl_3$ (5 mL). The mixture was stirred for 20 min, and the organic layer was separated and washed with 1 N NH_4OH and then with water. The organic layer was dried (Na_2SO_4) and evaporated in vacuo.

9a: Crystallized from petroleum ether (81%); mp 140–141 °C; CIMS (NH_3), m/e 487, 489 ($M + H^+$). Anal. ($C_{24}H_{27}N_2O_4Br$) C, H, N, Br. Oxalate: Crystallized from acetone; mp 245–247 °C dec. Anal. ($C_{24}H_{27}N_2O_4Br \cdot C_2H_2O_4$) C, H, N, Br.

9b: Crystallized from acetone (80%); mp 178–179 °C; CIMS (NH_3), m/e 489, 491 ($M + H^+$). Anal. ($C_{24}H_{29}N_2O_4Br$) C, H, N.

9c: Crystallized from petroleum ether (85%); mp 133–134 °C; CIMS (NH_3), m/e 501, 503 ($M + H^+$). Anal. ($C_{25}H_{29}N_2O_4Br \cdot 0.5H_2O$) C, H, N.

***N*-Alkyl-6,14-*endo*-etheno-7α-isothiocyanatotetrahydronororipavines (10a–c). General Procedure.** A mixture of the appropriate compound **7** (225 mg), $NaHCO_3$ (5 equiv), $CHCl_3$ (15 mL), and water (10 mL) was stirred vigorously and treated with redistilled thiophosgene (1.1 equiv). The mixture was stirred vigorously for 20 min, then the phases were separated, and the organic layer was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), and evaporated.

10a: Converted to the oxalate salt, which crystallized from acetone (80%); mp 238–239 °C dec; CIMS (NH_3), m/e 409 ($M + H^+$). Anal. ($C_{23}H_{24}N_2O_3S \cdot C_2H_2O_4$) C, H, N, S.

10b: Converted to the oxalate salt, which crystallized from acetone (94%); mp 237–238 °C dec; CIMS (NH_3), m/e 411 ($M + H^+$). Anal. ($C_{23}H_{26}N_2O_3S \cdot C_2H_2O_4 \cdot 0.5H_2O$) C, H, N, S.

10c: Converted to the oxalate and crystallized from isopropyl alcohol (78%); mp 229–229 °C dec; CIMS (NH_3), m/e 423 ($M + H^+$). Anal. ($C_{24}H_{26}N_2O_3S \cdot C_2H_2O_4$) C, H, N.

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