Effect of *N*-Alkyl and *N*-Alkenyl Substituents in Noroxymorphindole, 17-Substituted-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinans, on Opioid Receptor Affinity, Selectivity, and Efficacy

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Received November 28, 2000

The *N*-alkyl analogues (*N*-ethyl through *N*-heptyl), branched *N*-alkyl chain analogues (*N*-isopropyl, *N*-2-methylpropyl, and *N*-3-methylbutyl), and *N*-alkenyl analogues ((*E*)-*N*-3-methylallyl (crotyl), *N*-2-methylallyl, and *N*-3,3-dimethylallyl) were prepared in the noroxymorphindole series (17-substituted-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinans), and the effect of the *N*-substituent on opioid receptor affinity, selectivity, and efficacy was examined using receptor binding assays, [^{35}S]GTPγS efficacy determinations, and smooth muscle functional assays (electrically stimulated mouse vas deferens and guinea pig ileum). All of the compounds acted as opioid antagonists, including those with *N*-substituents which usually confer either weak agonist−antagonist behavior (*N*-ethyl) or potent opioid agonist activity (*N*-pentyl) in morphinan-like ligands which interact with the μ-receptor. Several *N*-substituted noroxymorphindoles were found to be more μ/δ-selective than naltrindole (NTI). The *N*-2-methylallylnoroxymorphindole, in particular, was found to be more selective than NTI in receptor binding assays (μ/δ = 1700 vs 120; κ/δ = 810 vs 140), as an antagonist in the GTPγS assay (μ/δ = 170 vs 140; κ/δ = 620 vs 160), and considerably more selective than NTI in the functional assays (μ/δ > 2200 vs 90). It also had high affinity for the δ-opioid receptor (K_i = 4.7 nM in the binding assay) and high antagonist potency (1.2 nM in the GTPγS assay; 8.9 nM in the MVD assay).

Introduction

Naltrindole (NTI, **1**)[1] is moderately selective (μ/δ affinity ratio = 120) and has very high affinity for the δ-receptor.[2] Since animal studies have revealed that δ-antagonists may be useful in the treatment of cocaine abuse,[3] and in the suppression of tolerance and dependence induced in mice by the μ-agonist morphine,[4] we, and others, have sought new δ-receptor antagonists more selective than NTI.

The *N*-cyclopropylmethyl group (*N*-CPM), the *N*-substituent in NTI (**1**; Chart 1), is probably responsible for opioid antagonist activity in both NTI and μ-opioid receptor ligands in the morphinan and 6,7-benzomorphan families. Studies indicate that the effect of varying the *N*-substituent at δ-receptors may be far different from their effect at μ-receptors. For example, (+)-4-[(α*R*)-α-(2*S*,5*R*)-4-allyl-2,5-dimethyl-1-piperazinyl)-3-methoxybenzyl]-*N*,*N*-diethylbenzamide (SNC 80), a selective and high-affinity δ-agonist, has an *N*-allyl substituent.[5,6] It, however, may act differently than *N*-CPM or *N*-allyl-substituted normorphinan-like compounds because its *N*-substituent has been theoretically determined, from the LMC δ-opioid recognition pharmacophore, to exist in a spatially different area of 3D space than that found for the protonated *N*-substituent in an oxymorphindole (OMI) or morphinan-like molecule.[7]

Examination[8] of the *N*-H, *N*-methyl, *N*-phenethyl, and *N*-cinnamyl analogues of NTI also indicates that the same *N*-substituent can induce different effects in ligands which tend to selectively interact with μ- or δ-opioid receptors. The *N*-H analogue, known to be a weak agonist in μ-receptor ligands, was, in noroxymorphindole, a full δ-receptor agonist, and the *N*-methyl derivative, which is generally a potent μ-receptor agonist in the morphinan or benzomorphan series, was a partial agonist or weak antagonist. In the pyrroloctahydroisoquinoline series, an *N*-ethyl analogue was found to be a δ-receptor-selective, high-affinity agonist,[9−11] in considerable contrast to the effect of that substituent in the 6,7-benzomorphan series.[12] These findings suggest that it is not possible to assume that *N*-substituents which induce agonist or antagonist behavior in morphinan-like molecules at the μ-receptor will act similarly in ligands which selectively interact with the δ-opioid receptor.

In light of these results, we decided to examine the effect of several different *N*-substituents (Chart 1) in

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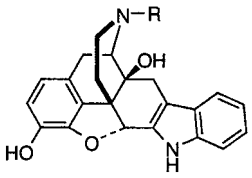
10.1021/jm000511w CCC: $20.00
Published on Web 03/30/2001

Chart 1. Structures of *N*-Substituted Noroxymorphindoles



Compound	R
1 (NTI)	$CH_2C_3H_5$ (CPM)
2	CH_2CH_3
3	$(CH_2)_2CH_3$
4	$(CH_2)_3CH_3$
5	$(CH_2)_4CH_3$
6	$(CH_2)_5CH_3$
7	$(CH_2)_6CH_3$
8	$CH(CH_3)_2$
9	$CH_2CH(CH_3)CH_3$
10	$CH_2CH_2CH(CH_3)_2$
11	$CH_2CH{=}CHCH_3$
12	$CH_2C(CH_3){=}CH_2$
13	$CH_2CH{=}C(CH_3)_2$

the noroxymorphindole molecule. The *N*-alkyl analogues (*N*-ethyl through *N*-heptyl **2**−**7**, respectively), *N*-alkenyl analogues ((*E*)-crotyl, 2-methylallyl, and 3,3-dimethylallyl **11**−**13**, respectively), and *N*-branched chain alkyl analogues (isopropyl, 2-methylpropyl, and 3-methylbutyl **8**−**10**, respectively) were evaluated in opioid receptor binding assays, and three of them were further examined in [^{35}S]GTPγS (efficacy) assays and bioassays.

Chemistry

Noroxymorphindole was prepared by treatment of noroxymorphone with phenylhydrazine, under conditions similar to those described by Portoghese et al.[8] Treatment of noroxymorphindole hydrochloride or the free base with the corresponding alkyl or alkenyl halide in the presence of K_2CO_3 or $NaHCO_3$ in DMF afforded the desired *N*-substituted product in moderate to good yields.

Results and Discussion

The affinities of the noroxymorphindole analogues for μ-, κ-, and δ-opioid receptors are summarized in Table 1. These data indicate that replacement of the *N*-CPM group of NTI with the various *N*-substituents, shown in Chart 1, caused major changes in selectivity and affinity for the δ-receptor. All of the analogues **2**−**13** had higher affinity at the δ-opioid receptor than at μ- or κ-receptors, and their μ/δ-selectivity was generally as good as, or considerably better than, that of NTI. Although all of the analogues showed less affinity for the δ-opioid receptor than NTI, the ethyl (**2**), propyl (**3**), butyl (**4**), 2-methylpropyl (**9**), 3-methylbutyl (**10**), (*E*)-crotyl (**11**), and 2-methylallyl (**12**) analogues still had relatively high δ-affinity (K_i < 10 nM).

With the exception of the *N*-propyl analogue **3** which had higher affinity than the smaller ethyl analogue **2**, both affinity and selectivity for the δ-receptor were inversely affected as the length of the *N*-alkyl chain increased. For the straight chain alkyl groups, the *N*-propyl analogue **3** gave the highest δ-receptor affinity (K_i = 2.0 nM), and among those compounds with the straight chain alkyl groups the greatest δ-selectivity was observed with the *N*-ethyl substituent (μ/δ = 500). Introduction of unsaturation in the *N*-substituent affected selectivity much more than affinity for the δ-receptor. For example, the selectivity of the 2-methylallyl analogue **12** (μ/δ = 1700) was 10 times greater than that of the (*E*)-*N*-crotyl analogue **11** (μ/δ = 160), although both of these compounds had similarly high δ-receptor affinities (K_i = 4.7 and 7.4 nM, respectively). The 2-methylallyl compound **12** proved to be the most selective δ-antagonist, exceeding the μ/δ selectivity of NTI more than 14-fold. The introduction of branching in the alkyl chain caused a noticeable shift in δ-affinity. Interestingly, unlike the straight chain alkyls, as the size of the branched chain analogues increased (from **8** to **9** or **10**), the affinity increased as well. Thus, the two larger branched chain compounds we evaluated, the 2-methylpropyl analogue **9** and the 3-methylbutyl analogue **10**, had 7−8-fold higher δ-affinity than the smallest branched chain compound, the isopropyl analogue **8** (K_i = 3.8 and 4.8 vs 33 nM). Whereas compounds **8** and **10** of the branched chain analogues had μ/δ-selectivity similar to that of NTI, analogue **9** showed remarkably higher μ/δ-selectivity (680), but its κ/δ-selectivity was only slightly better than that in NTI.

The [^{35}S]GTPγS functional binding assays (Table 2) were carried out on three of the more interesting compounds: **2**, **11**, and **12**. These compounds were chosen because they had good selectivity and affinity for the δ-receptor and they had the least affinity for the other opioid receptors which, we hoped, would tend to

Table 1. Opioid Receptor Binding Affinity of *N*-Substituted NTI Analogues

	$K_i \pm$ SEM (nM)			selectivity ratio	
compd	μ^a	δ^b	κ^c	μ/δ	κ/δ
1 (NTI)[d]	27 ± 1.3	0.22 ± 0.05	30 ± 3.6	120	140
OMI	66 ± 5.6	0.80 ± 0.10	*e*	80	*e*
2	2500 ± 240	5.0 ± 0.8	3000 ± 190	500	600
3	710 ± 44	2.0 ± 0.4	380 ± 19	360	190
4	1300 ± 110	8.4 ± 1.6	900 ± 49	160	110
5	2800 ± 170	16 ± 3.0	2000 ± 85	180	130
6	4600 ± 480	26 ± 3.5	3100 ± 220	180	120
7	4600 ± 200	79 ± 4.7	>7000	60	>90
8	>6600	33 ± 5.0	6200	>200	190
9	2600 ± 210	3.8 ± 0.1	650 ± 25	680	170
10	1300 ± 49	4.8 ± 0.3	670 ± 76	270	140
11	1200 ± 40	7.4 ± 1.0	960 ± 55	160	130
12	7900 ± 820	4.7 ± 0.9	3800 ± 220	1700	810
13	2800 ± 320	25 ± 2.3	3200 ± 170	110	130

[a] Displacement of [^{3}H]DAMGO. [b] Displacement of [^{3}H]DADLE. [c] Displacement of [^{3}H]U69,593. [d] See ref 5. [e] Not determined.

Table 2. Antagonist Activity of *N*-Ethyl (**2**), *N*-Crotyl (**11**), and *N*-Methylallyl (**12**) Noroxymorphindole Analogues on Agonist-Stimulated GTPγ^{35}S Binding

	$K_i \pm$ SD (nM)			selectivity ratio	
compd	μ^a (MOR)	δ^b (DOR)	κ^c (KOR)	μ/δ	κ/δ
1 (NTI)[d]	4.3 ± 0.5	0.03 ± 0.003	4.7 ± 3.0	140	160
2	290 ± 71	3.2 ± 0.9	>1000	90	>310
11	30 ± 5	0.68 ± 0.09	118 ± 20	40	170
12	200 ± 44	1.2 ± 0.3	740 ± 140	170	620

[a] Apparent functional K_i[17] (vs 1 μM DAMGO). [b] Apparent functional K_i[17] (vs 200 nM SNC 80). [c] Apparent functional K_i[17] (vs 2 μM U50,488H). [d] See ref 5.

Table 3. Antagonist Activity of *N*-Ethyl (**2**), *N*-Crotyl (**11**), and *N*-Methylallyl (**12**) Noroxymorphindole Analogues in Mouse Vas Deferens and Guinea Pig Ileum Preparations

	activity in MVD		activity in GPI/LMMP		
compd	agonist[b]	antagonist[c] K_e (nM)	agonist[b]	antagonist[d] K_e (nM)	selectivity ratio: μ/δ
1 (NTI)[a]	16% (1 μM)	0.49	18% (1 μM)	43	90
2	9% (100 nM)	9.6 ± 2.4	1.2% (1 μM)	96 ± 23	10
11	12% (100 nM)	26 ± 5	22% (1 μM)	5500 ± 1900	210
12	18% (100 nM)	8.9 ± 2.6	63% (20 μM)	>20 μM	>2200

[a] See ref 18. [b] Percent (%) inhibition of contraction height. [c] Tested with DPDPE. [d] Tested with PL-017.

lessen or eliminate effects caused by an interaction with those receptors. Initial tests revealed that these compounds possessed no agonist activity at a single concentration of 10 μM. Accordingly, the ability of these compounds to inhibit GTPγS binding in cloned opioid receptors stimulated by DAMGO, a μ-receptor agonist, SNC 80, a δ-receptor agonist, and U50,488H, a κ-receptor agonist, was determined, and the results are summarized in Table 2. The GTPγS data revealed that the 2-methylallyl compound **12** was a selective and potent δ-antagonist. The (*E*)-*N*-crotyl compound **11** was the most potent δ-antagonist; however, it was much less selective than **12**. The *N*-ethyl analogue **2** proved to be less potent but showed high κ/δ-selectivity (>310).

Compounds **2**, **11**, and **12** were also subjected to two other functional assays (Table 3): the GPI assay (guinea pig ileum longitudinal muscle myenteric plexus (GPI/LMMP), which has mostly μ-opioid receptors) and the electrically induced smooth muscle contraction of mouse vas deferens (MVD, which has mostly δ-receptors). Differences were seen between the assays. The reasons for the obtained selectivity differences are not clear, but it is apparent that in the MVD assay all three analogues were found to exhibit δ-opioid antagonist activity. Compound **2** exhibited poor μ/δ-selectivity, whereas compound **11** was more selective but significantly less potent (50 times less potent than NTI). *N*-2-Methylallylnoroxymorphindole (**12**), on the other hand, which exhibited only a μ/δ-selectivity comparable to that of NTI in the GTPγS assay (Table 2), showed outstanding μ/δ-selectivity (>2200) in the smooth muscle functional assays (Table 3). It was >24 times more selective than NTI; however, it showed more agonist activity and lower affinity than NTI in the MVD assay. The GPI assay indicated that **12** had less agonist activity at the μ-receptor than NTI.

It appears that modification of the *N*-substituent in noroxymorphindole caused major changes in affinity, selectivity, and potency of the ligand. It is also apparent that the effect of some *N*-substituents (e.g. *N*-ethyl or *N*-pentyl) is dissimilar in ligands selective for δ- or μ-opioid receptors. The derivative with an alkenyl moiety bearing a methyl group in an area of 3D space which might provide some degree of bulkiness in the vicinity of both the nitrogen atom and the double bond in the side chain, the 2-methylallyl analogue **12**, had the highest overall selectivity of all tested derivatives and was significantly superior to NTI in the binding and functional assays. The outstanding properties of 17-(2-methylallyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (**12**) make it worthy of further investigation. It is remarkable that a minor change in chemical structure (the 2-methallyl analogue **12** is a constitutional isomer of NTI) could lead to an interesting alteration in pharmacological profile, although it is now clear that ostensibly minor structural changes in the *N*-substituent can influence the pharmacological effect of compounds interacting with either the μ- or δ-opioid receptors in unanticipated ways.

Experimental Section

TLC, spectra, mp, and CHN were obtained as noted.[2]

6,7-Dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (Noroxymorphindole) Hydrochloride. A suspension of noroxymorphone (8.89 g, 30.9 mmol) and phenylhydrazine hydrochloride (4.47 g, 30.9 mmol) in MeOH (65 mL) and 3 M aqueous HCl (65 mL) was heated at 65 °C for 18 h. The mixture was allowed to reach room temperature, and the precipitate was filtered off and washed 2× with H_2O. Thorough drying in vacuo afforded 12.3 g (99%) of noroxymorphindole hydrochloride: mp > 250 °C dec (lit. mp > 250 °C).[8]

General Procedure A: Preparation of Compounds 3−10 and 13. To a stirred solution of *N*-noroxymorphindole free base (300 mg, 0.83 mmol) in DMF (3 mL) was added Na_2CO_3 (102 mg, 0.96 mmol) followed by the addition of the appropriate alkyl or alkenyl halide (0.87 mmol). The resulting heterogeneous reaction mixture was heated to 90 °C and allowed to stir at that temperature for 2.5 h. Upon completion of the reaction (TLC), the reaction mixture was cooled to room temperature and filtered. The filtrate was evaporated to dryness and the residue was dissolved in $CHCl_3$ and subjected to flash chromatography to give an off-white solid product.

17-Propyl-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (3): 56%; R_f 0.37 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 210 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.24 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.27 (d, J = 7.8 Hz, 1H), 7.14 (dt, J = 8.0 1.2 Hz, 1H), 7.01 (dt, 1J = 7.8 1.2 Hz, 1H), 6.51 (dd, J = 8.1 1.2 Hz, 2H), 5.71 (s, 1H); MS m/z = 403 (M + 1). Anal. ($C_{25}H_{26}N_2O_3$·0.75H_2O) C, H, N.

17-Butyl-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (4): 54%; R_f 0.45 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 215 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.24 (d, J = 7.8 Hz, 1H), 7.11 (dt, J = 8.4 0.9 Hz, 1H), 7.00 (m, 1H), 6.42 (dd, J = 8.1 Hz, 2H), 5.78 (s, 1H); MS m/z = 417 (M + 1). Anal. ($C_{26}H_{29}N_2O_3$-Cl·1.25H_2O) C, H, N.

17-Pentyl-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (5): 66%; R_f 0.48 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) 220 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H), 7.40 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 8.1 Hz, 1H), 7.11 (dt, J = 8.4 0.9 Hz, 1H), 7.00 (m, 1H), 6.49 (dd, J = 8.1 Hz, 2H), 5.74 (s, 1H); MS m/z = 431 (M + 1). Anal. ($C_{27}H_{31}N_2O_3Cl$·1.25H_2O) C, H, N.

17-Hexyl-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (6): 61%; R_f 0.44 (C/M/A, 10:1:0.1, v/v); mp 160−165 °C; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.15 (dt, J = 8.4 0.9 Hz, 1H), 7.07 (m, 1H), 6.45 (dd, J = 8.1 Hz, 2H), 5.64 (s, 1H); MS m/z = 445 (M + 1). Anal. ($C_{28}H_{32}N_2O_3$·0.75H_2O) C, H, N.

17-Heptyl-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (7): 49%; R_f 0.53 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 200 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.40 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 1H), 7.12 (dt, J = 8.4 0.9 Hz, 1H), 7.09 (m, 1H), 6.47 (dd, J = 8.1 Hz, 2H), 5.69 (s, 1H); MS m/z = 459 (M + 1). Anal. ($C_{29}H_{35}N_2O_3$-Cl·0.75H_2O) C, H, N.

17-(1-Methylethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (8): 62%; R_f 0.37 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 195 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.38 (s, 1H), 7.41 (d, J = 7.8 Hz, 1H), 7.25 (d, J = 7.8 Hz, 1H), 7.17 (t, J = 8.4, 1H), 7.07 (m, 1H), 6.45 (dd, J = 8.1 Hz, 2H), 5.71 (s, 1H); MS m/z = 403 (M + 1). Anal. ($C_{25}H_{26}N_2O_3$·1.0H_2O) C, H, N.

7-(2-Methylpropyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (9): 47%; R_f 0.36 (C/M/A, 10:1:0.1, v/v); mp > 170 °C dec; ^{1}H NMR ($CDCl_3$) δ 8.42 (s,

1H), 7.40 (d, $J = 7.8$ Hz, 1H), 7.21 (d, $J = 8.1$ Hz, 1H), 7.09 (t, $J = 7.5$, 1H), 6.99 (t, $J = 7.5$ Hz, 1H), 6.50 (d, $J = 8.1$ Hz, 1H), 6.41 (d, $J = 8.1$ Hz, 1H), 5.75 (s, 1H), 0.95 (t, $J = 6.6$ Hz, 3H); MS $m/z = 417$ (M + 1). Anal. ($C_{26}H_{28}N_2O \cdot 1.5H_2O$) C, H, N.

17-(3-Methylbutyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (10): 58%; R_f 0.46 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 170 °C dec; ^{1}H NMR (DMSO-d_6) δ 8.85 (s, 1H), 7.31 (m, 2H), 7.06 (t, $J = 8.4$ Hz, 1H), 6.92 (t, $J = 8.1$ Hz, 1H), 6.50 (m, 2H), 5.50 (s, 1H); MS $m/z = 431$ (M + 1). Anal. ($C_{27}H_{31}N_2O_3Cl \cdot 0.5H_2O$) C, H, N.

17-(3-Methyl-2-butenyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (13): 47%; R_f 0.47 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 220 °C; ^{1}H NMR ($CDCl_3$) δ 8.37 (s, 1H), 7.37 (d, $J = 7.5$ Hz, 1H), 7.22 (d, $J = 8.1$ Hz, 1H), 7.10 (t, $J = 7.2$, 1H), 6.99 (t, $J = 7.5$, 1H), 6.56 (d, $J = 8.4$ Hz, 1H) 6.48 (d, $J = 8.1$ Hz, 1H), 5.69 (s, 1H), 5.20 (bs, 1H), 1.76 (s, 3H), 1.68 (s, 3H); MS $m/z = 429$ (M + 1). Anal. ($C_{27}H_{28}N_2O_3 \cdot 0.75H_2O$) C, H, N.

General Procedure B (proved most satisfactory): Multigram Synthesis of Compounds 2, 11, and 12. To a stirred solution of *N*-noroxymorphindole hydrochloride (1.00 g, 2.52 mmol) in anhydrous DMF (20 mL) was added $NaHCO_3$ (529 mg, 6.30 mmol) followed by addition of the appropriate alkyl or alkenyl halide (2.65 mmol). The resulting heterogeneous reaction mixture was heated to 90 °C and allowed to stir at that temperature for 2.5 h (compounds **11** and **12**) or 18 h (compound **2**). After evaporation of the solvent, the residue was partitioned between NH_4OH and $CHCl_3$, and the aqueous layer was extracted 4× with $CHCl_3$. The combined organic layers were washed 2× with brine, dried (Na_2SO_4), filtered and evaporated to dryness. The off-white solid residue was treated with aqueous 2 N HCl/ethanol to obtain the hydrochloride as colorless crystals.

17-Ethyl-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (2): 84%; R_f (free base) 0.33 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 210 °C dec; ^{1}H NMR (HCl salt) (DMSO-d_6) δ 7.35 (d, $J = 7.8$ Hz, 1H), 7.33 (d, $J = 7.8$ Hz, 1H), 7.11 (t, $J = 8.0$ Hz, 1H), 6.96 (t, $J = 8.0$ Hz, 1H), 6.67 (d, $J = 8.1$ Hz, 1H), 6.58 (d, $J = 8.1$ Hz, 1H), 5.68 (s, 1H); MS $m/z = 389$ (M + 1). Anal. ($C_{24}H_{25}N_2O_3Cl \cdot 0.5H_2O$) C, H, N.

(*E*)-17-(2-Butenyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (11): 81%; R_f (free base) 0.51 (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 195 °C dec; ^{1}H NMR (free base) ($CHCl_3$) δ 7.38 (d, $J = 7.8$ Hz, 1H), 7.21 (d, $J = 7.8$ Hz, 1H), 7.09 (t, $J = 8.0$ Hz, 1H), 6.98 (t, $J = 8.0$ Hz, 1H), 6.56 (d, $J = 8.1$ Hz, 1H), 6.43 (d, $J = 8.1$ Hz, 1H), 5.71 (s, 1H); 5.64 (m, 1H), 5.46 (m, 1H); MS $m/z = 415$ (M + 1). Anal. ($C_{26}H_{27}N_2O_3Cl \cdot 0.5H_2O$) C, H, N.

17-(2-Methyl-2-propenyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7:2′,3′-indolomorphinan (12): 83%; R_f 0.57 (free base) (C/M/A, 10:1:0.1, v/v); mp (HCl salt) > 200 °C dec; ^{1}H NMR (HCl salt) (DMSO-d_6) δ 7.38 (d, $J = 7.8$ Hz, 1H), 7.36 (d, $J = 7.8$ Hz, 1H), 7.11 (t, $J = 8.0$ Hz, 1H), 6.96 (t, $J = 8.0$ Hz, 1H), 6.65 (d, $J = 8.1$ Hz, 1H), 6.58 (d, $J = 8.1$ Hz, 1H), 5.69 (s, 1H); 5.38 (bs, 2H); MS $m/z = 415$ (M + 1). Anal. ($C_{26}H_{27}N_2O_3Cl \cdot 0.5H_2O$) C, H, N.

Biological Assays.[13−17] Details provided in the Supporting Information.

Acknowledgment. The authors thank Mallinckrodt for the generous gift of noroxymorphone, Robert Horel (NIDA, NIH) for his expert technical assistance, and Noel Whittaker (NIDDK, NIH) who provided all mass spectroscopy data reported.

Supporting Information Available: Microelemental analyses (C, H, N) and biological assays as modified. This material is available free of charge via the Internet at http://pubs.acs.org.

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JM000511W