vacuo to give a brown oil. Purification by flash column chromatography through silica gel afforded 9.0 g (49% yield) of the desired aldehyde: mp 57–58 °C. Anal. ($C_{17}H_{13}NO_2$) C, H, N.

3-[[3-(2-Quinolinylmethoxy)phenyl]ethenyl]benzonitrile (10a). To a suspension of 8.18 g (17.85 mmol) of (3-cyanobenzyl)triphenylphosphonium bromide in 100 mL of DMF at 0 °C under an N_2 atmosphere was added 0.67 g (22.31 mmol, 1.25 equiv) of 80% NaH in oil dispersion. The mixture was stirred at 0 °C for 15 min followed by 1 h at room temperature. The reaction was recooled at 0 °C and 4.7 g (17.85 mmol) of aldehyde **9** in 20 mL of DMF was added dropwise over a period of 15 min. After addition, the reaction was stirred at 25 °C for 2 h and then poured into ice water. The precipitate that formed was filtered off, redissolved in CH_2Cl_2, dried, concentrated in vacuo, and then purified by flash column chromatography through silica gel to afford 4.73 g (73%) of the nitrile: mp 115–117 °C.

5-[[3-[3-(2-Quinolinylmethoxy)phenyl]ethenyl]phenyl]-1*H*-tetrazole (10). A solution of 1 g (2.76 mmol) of nitrile **10a**, 0.90 g (13.80 mmol, 5 equiv) of NaN_3, and 1.59 g (13.80 mmol, 5 equiv) of pyridine hydrochloride in 15 mL of DMF was heated at 100 °C for 48 h. The reaction mixture was poured into ice water and allowed to stand for 48 h. The precipitate that formed was filtered off and recrystallized from hot MeOH to afford 0.5 g (45% yield) of the desired tetrazole in the form of a beige, crystalline solid: mp 117–118 °C. Anal. ($C_{25}H_{19}N_5O$) C, H, N.

5-[3-[2-[3-(2-Quinolinylmethoxy)phenyl]ethyl]phenyl]-1*H*-tetrazole (39). (a) 3-[2-[3-(2-Quinolinylmethoxy)-phenyl]ethyl]benzonitrile (39a). A mixture of 2.0 g (5.52 mmol) of olefin **10a** and 0.2 g of 10% Pd/C in 50 mL of EtOH was hydrogenated at 30 psi for 4 h. The mixture was filtered through Celite and the filtrate was concentrated in vacuo. Purification by flash column chromatography through silica gel gave a clear oil. Crystallization from Et_2O/hexane afforded 1.1 g (55%) of the desired nitrile in the form of a white, crystalline solid: mp 49–50 °C.

(b) Compound 39. To a solution of 1.07 g (2.94 mmol) of nitrile **39a** in 20 mL of DMF was added 0.95 g (14.68 mmol, 5 equiv) of NaN_3 and 0.78 g (14.68 mmol, 5 equiv) of NH_4Cl. The mixture was heated at 100 °C for 48 h, then poured into ice water. The resulting precipitate was filtered off, recrystallized from MeOH/H_2O, and finally recrystallized from CH_2Cl_2/Et_2O to afford 0.60 g (50%) of the desired tetrazole in the form of a white, crystalline solid: mp 126–129 °C. Anal. ($C_{25}H_{21}N_5O \cdot 1.75H_2O$) C, H, N.

Biological Assays. All biological assays are described in the first paper of this series.[1]

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Registry No. **3a**, 107432-15-5; **3b**, 124993-40-4; **3b** (7-chloro derivative), 124993-50-6; **6a**, 123226-28-8; **6b**, 123226-29-9; **6c**, 124993-41-5; **9**, 103119-21-7; **10**, 124993-42-6; **10a**, 124993-54-0; **11a**, 4752-58-3; **11b**, 125023-19-0; **12**, 123225-66-1; **13**, 123225-67-2; **14**, 123225-63-8; **15**, 123225-57-0; **16**, 123225-64-9; **17**, 124993-43-7; **18**, 123225-76-3; **19**, 123225-81-0; **20**, 123225-82-1; **21**, 123225-80-9; **22**, 123225-69-4; **23**, 123247-25-6; **24**, 123225-72-9; **25**, 123225-73-0; **26**, 123225-95-6; **27**, 120128-20-3; **27a**, 124993-48-2; **27b**, 124993-49-3; **28**, 123225-97-8; **29**, 123225-98-9; **30**, 123247-23-4; **31**, 123226-00-6; **31a**, 123226-39-1; **31b**, 124993-51-7; **31c**, 124993-52-8; **32**, 123225-56-9; **32a**, 123225-79-6; **33**, 123226-27-7; **34**, 123225-58-1; **35**, 124993-44-8; **36**, 123225-60-5; **37**, 123225-96-7; **38**, 124993-45-9; **39**, 123692-28-4; **39a**, 124993-55-1; **40**, 123226-06-2; 41, 124993-46-0; **42**, 124993-47-1; 3-HOC_6H_4CN, 873-62-1; 4-HOC_6H_4CN, 767-00-0; 2-$ClCH_2C_6H_4CH_2Cl$, 612-12-4; 3-$ClCH_2C_6H_4CH_2Cl$, 626-16-4; 4-$ClCH_2C_6H_4CH_2Cl$, 623-25-6; 2-$HOC_6H_4CH_2OH$, 90-01-7; $BrCH_2CN$, 590-17-0; 3-$HOC_6H_4CH_2OH$, 620-24-6; 4-$HOC_6H_4CH_2OH$, 623-05-2; 4-HO-2-$MeOC_6H_4CN$, 84224-29-3; 3-HO-5-$MeOC_6H_4CN$, 124993-53-9; 3-HOC_6H_4CHO, 100-83-4; 3-$NCC_6H_4CH_2P^+Ph_3 \cdot Br^-$, 24722-19-8; 2-(chloromethyl)quinoline hydrochloride, 3747-74-8.

Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 3.[1] Extensive Study on Cyprodime-Related Compounds

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A series of cyprodime-related compounds (**2**, 4–12, and **26**) has been synthesized and evaluated for opioid agonist and antagonist activity with the mouse vas deferens and guinea pig ileum preparations. None of the changes to cyprodime, including the introduction of a 3-OMe group, increasing and decreasing the size of or completely removing the substituent in position 4, replacing the *N*-cyclopropylmethyl group with an *N*-allyl group, or replacing the 14-OMe with a 14-OEt substituent, resulted in an improved μ antagonist profile and most were detrimental either in terms of μ selectivity and potency or increased agonist activity. Increasing the length of the substituent in position 4 resulted in a compound (**6a**) with a very similar profile to that of cyprodime.

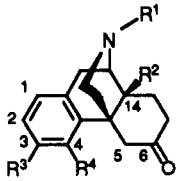
Cyprodime (**1**, Chart I) was found to be a pure opioid antagonist with high selectivity for μ receptors.[1,2] Since cyprodime has the highest μ selectivity of nonpeptide, competitive μ opioid antagonists reported, this ligand is of interest as a pharmacological tool in opioid research. In an attempt to enhance the μ potency and/or μ selectivity of cyprodime while retaining its antagonist purity and in order to further elaborate on structure–activity relationships of 14-alkoxymorphinans, we prepared the *N*-allyl analogue of cyprodime (compound **2**), its 4-hydroxy analogue **4** (a possible metabolite of cyprodime), aromatic unsubstituted derivative **5**, its 4-isopropyloxy analogue **6**, its 4-*n*-butoxy analogue **6a**, 3,4,14-trimethoxy derivatives

† Institute of Organic and Pharmaceutical Chemistry.
‡ Reckitt & Colman.

(1) Part 2 of this series: Schmidhammer, H.; Burkard, W. P.; Eggstein-Aeppli, L.; Smith, C. F. C. *J. Med. Chem.* **1989**, *32*, 418.
(2) H. Schmidhammer In *Trends in Medicinal Chemistry '88*; van der Goot, H., Domany, G., Pallos, L., Timmerman, H., Eds.; Elsevier Science Publishers B. V.; Amsterdam, 1989.

0022-2623/90/1833-1200$02.50/0

Chart I



1: $R^1 = CH_2CH(CH_2)_2$, $R^2 = R^4 = OCH_3$, $R^3 = H$ (cyprodime)
2: $R^1 = CH_2CH{=}CH_2$, $R^2 = R^4 = OCH_3$, $R^3 = H$
3: $R^1 = R^3 = H$, $R^2 = R^4 = OCH_3$
4: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$, $R^3 = H$, $R^4 = OH$
5: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$, $R^3 = R^4 = H$
6: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$, $R^3 = H$, $R^4 = OCH(CH_3)_2$
6a: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$, $R^3 = H$, $R^4 = O(CH_2)_3CH_3$
7: $R^1 = CH_2CH(CH_2)_2$, $R^2 = R^3 = R^4 = OCH_3$
8: $R^1 = CH_2CH{=}CH_2$, $R^2 = R^3 = R^4 = OCH_3$
9: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OC_2H_5$, $R^3 = H$, $R^4 = OCH_3$
10: $R^1 = CH_2CH{=}CH_2$, $R^2 = OC_2H_5$, $R^3 = H$, $R^4 = OCH_3$
11: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OC_2H_5$, $R^3 = R^4 = OCH_3$
12: $R^1 = CH_2CH{=}CH_2$, $R^2 = OC_2H_5$, $R^3 = R^4 = OCH_3$
13: $R^1 = CH_3$, $R^2 = OCH_3$, $R^3 = H$, $R^4 = OH$
14: $R^1 = CH_3$, $R^2 = OCH_3$, $R^3 = H$, $R^4 = O(CH_2)_3CH_3$
15: $R^1 = CO_2CHClCH_3$, $R^2 = OCH_3$, $R^3 = H$, $R^4 = O(CH_2)_3CH_3$
16: $R^1 = R^3 = H$, $R^2 = OCH_3$, $R^4 = O(CH_2)_3CH_3$
17: $R^1 = CH_3$, $R^2 = R^3 = R^4 = OCH_3$
18: $R^1 = CO_2CH_2CCl_3$, $R^2 = R^3 = R^4 = OCH_3$
19: $R^1 = H$, $R^2 = R^3 = R^4 = OCH_3$

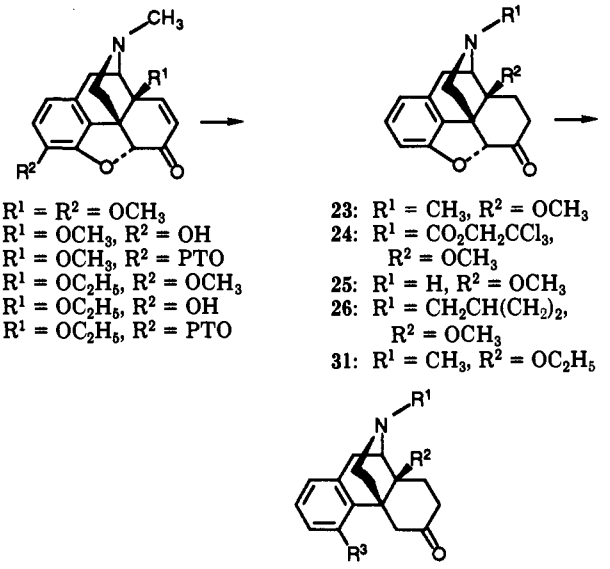
7 and 8, 14-ethoxy derivatives 9–12, and 4,5-epoxy derivative 26.

Chemistry

Compound 2, the *N*-allyl analogue of cyprodime (1), was prepared from *N*-normorphinan 3 by an analogous procedure as described for cyprodime.[1]

Phenol 4, a possible metabolite of cyprodime, and aromatic unsubstituted morphinan 5 were prepared by starting from epoxymorphinanone 23, which was synthesized by a different and more efficient route as described in a previous publication.[3] Instead of starting from oxymorphone, as described in the previous paper,[3] we went out from 14-*O*-methylcodeinone (20).[4] Ether cleavage of 20 with 48% HBr afforded phenol 21. In order to remove the phenolic hydroxyl group, compound 21 was treated with 5-chloro-1-phenyl-1*H*-tetrazole[5] in DMF in the presence of K_2CO_3 to give phenyltetrazolyl ether 22, which was hydrogenated in AcOH over Pd/C to afford compound 23. *N*-Demethylation was accomplished with 2,2,2-trichloroethyl chloroformate.[6] Carbamate 24 was cleaved with Zn in diluted AcOH to give *N*-normorphinan 25, which was alkylated with cyclopropylmethyl chloride to afford 26. Reductive cleavage of the 4,5-oxygen bridge was achieved with Zn/NH_4Cl[7,8] in refluxing MeOH to yield 4. This phenol (4) could be O-methylated with phenyltrimethylammonium chloride in DMF in the presence of K_2CO_3 to give cyprodime (1) by a different route as described in a previous paper.[1] Removal of the hydroxyl group of 4 was accomplished via phenyltetrazolyl ether 27, which was hydrogenated over Pd/C in AcOH to give aromatic unsubstituted morphinanone 5 (Scheme I).

Scheme I[a]



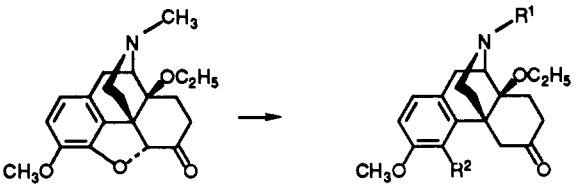
20: $R^1 = R^2 = OCH_3$
21: $R^1 = OCH_3$, $R^2 = OH$
22: $R^1 = OCH_3$, $R^2 = PTO$
28: $R^1 = OC_2H_5$, $R^2 = OCH_3$
29: $R^1 = OC_2H_5$, $R^2 = OH$
30: $R^1 = OC_2H_5$, $R^2 = PTO$

23: $R^1 = CH_3$, $R^2 = OCH_3$
24: $R^1 = CO_2CH_2CCl_3$, $R^2 = OCH_3$
25: $R^1 = H$, $R^2 = OCH_3$
26: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$
31: $R^1 = CH_3$, $R^2 = OC_2H_5$

4: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$, $R^3 = OH$
27: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$, $R^3 = PTO$
5: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$, $R^3 = H$
32: $R^1 = CH_3$, $R^2 = OC_2H_5$, $R^3 = OH$
33: $R^1 = CH_3$, $R^2 = OC_2H_5$, $R^3 = OCH_3$
34: $R^1 = CO_2CHClCH_3$, $R^2 = OC_2H_5$, $R^3 = OCH_3$
35: $R^1 = H$, $R^2 = OC_2H_5$, $R^3 = OCH_3$
9: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OC_2H_5$, $R^3 = OCH_3$
10: $R^1 = CH_2CH{=}CH_2$, $R^2 = OC_2H_5$, $R^3 = OCH_3$

[a] PTO = phenyltetrazolyloxy.

Scheme II



36

37: $R^1 = CH_3$, $R^2 = OH$
38: $R^1 = CH_3$, $R^2 = OCH_3$
39: $R^1 = CO_2CHClCH_3$, $R^2 = OCH_3$
40: $R^1 = H$, $R^2 = OCH_3$
11: $R^1 = CH_2CH(CH_2)_2$, $R^2 = OCH_3$
12: $R^1 = CH_2CH{=}CH_2$, $R^2 = OCH_3$

The isopropyloxy analogue of cyprodime (compound 6) was synthesized from phenol 4 by alkylation with isopropyl bromide in DMF in the presence of NaH.

Compound 6a, the 4-*n*-butoxy analogue of cyprodime, was prepared by starting from 4-hydroxymorphinan 13. 4-O-Alkylation with butyl bromide in DMF using NaH as base gave 14, which was N-demethylated via carbamate 15 to yield *N*-nor derivative 16. Alkylation with cyclopropylmethyl chloride in DMF afforded 6a.

The 3,4,14-trimethoxy derivatives 7 and 8 were synthesized starting from *N*-methyl-3,4,14-trimethoxymorphinan-6-one (17).[3] *N*-Demethylation of 17 using 2,2,2-trichloroethyl chloroformate gave carbamate 18, which was cleaved reductively with Zn/NH_4Cl in refluxing MeOH. *N*-Normorphinan 19 was alkylated with either cyclopropylmethyl chloride or allyl bromide in DMF in the presence of K_2CO_3 to yield 7 and 8, respectively.

14-Ethoxy derivatives 9–12 were synthesized with 14-ethoxycodeinone (28)[4] as starting material. To obtain the 4-monomethoxy derivatives 9 and 10, first ether cleavage with 48% HBr was accomplished to afford phenol 29. The

(3) Schmidhammer, H.; Aeppli, L.; Atwell, L.; Fritsch, F.; Jacobson, A. E.; Nebuchla, M.; Sperk, G. *J. Med. Chem.* **1984**, *27*, 1575.
(4) Kobylecki, R. J.; Carling, R. W.; Lord, J. A. H.; Smith, C. F. C.; Lane, A. C. *J. Med. Chem.* **1982**, *25*, 116.
(5) Musliner, W. J.; Gates, J. W. *J. Am. Chem. Soc.* **1966**, *88*, 4271.
(6) Montzka, T. A.; Matiskella, J. D.; Partyka, R. A. *Tetrahedron Lett.* **1974**, *14*, 1325.
(7) Schöpf, C.; Pfeifer, T. *Liebigs Ann. Chem.* **1930**, *483*, 157.
(8) Beyerman, H. C.; van Bommel, L.; Maat, L.; Olieman, C. *Recl. Trav. Chim. Pays-Bas* **1976**, *95*, 189.

Table I. Opioid Antagonist Activities of Cyprodime and Its Analogues in the MVD

compd	K_e[a], nM ± SEM			selectivity ratio	
	NM[b] (μ)	EKC[c] (κ)	DADLE[d] (δ)	κ/μ	δ/μ
2	230 ± 7.3	6041 ± 118	6451 ± 880	26	28
6	108 ± 20	2413 ± 70	11300 ± 950	22	105
6a	21 ± 2.7	811 ± 238	2050 ± 730	39	98
7	120 ± 11	2097 ± 190	744 ± 20	17	6
8	118 ± 15	3900 ± 1800	179 ± 18	33	1.5
9	21.7 ± 2.7	1132 ± 292	2127 ± 366	52	98
10	81 ± 17	2562 ± 830	3742 ± 1060	32	46
11	46 ± 9	5300 ± 2200	1537 ± 19	115	33
12	184 ± 48	6194 ± 440	665 ± 88	34	3.6
26	168 ± 24	648 ± 15	4026 ± 136	3.9	24
cyprodime	55.4 ± 4	1551 ± 448	6108 ± 205	28	110
naloxone	1.4 ± 0.1	15.9 ± 6.7	9.6 ± 2.3	12	7

[a] K_e = [antagonist]/DR − 1, where DR is dose ratio (i.e. ratio of equiactive concentrations of the test agonist in the presence and absence of the antagonist. The present K_e values were obtained with concentrations of the antagonists which produced a dose ratio of between 3 and 10 against the relevant agonist. A minimum of two determinations was made for each K_e value. [b] NM = normorphine. [c] EKC = ethylketocyclazocine. [d] DADLE = [D-Ala^2, D-Leu^5]enkephalin.

3-OH group was removed via tetrazolyl ether **30**. Reductive opening of the 4,5-oxygen bridge of **31** gave phenol **32**, which was first 4-O-methylated with phenyltrimethylammonium chloride to afford compound **33**, which was *N*-demethylated with 1-chloroethyl chloroformate.[9] Carbamate **34** was refluxed in MeOH to yield **35**. *N*-Nor derivative **35** was alkylated with cyclopropylmethyl chloride (to yield **9**) and allyl bromide (to give **10**) (Scheme I).

For the synthesis of 3,4-dimethoxy derivatives **11** and **12**, 14-ethoxycodeinone (**28**) was first hydrogenated, following the published procedure,[4] to give 14-*O*-ethyloxycodone (**36**). The following reaction sequence (see Scheme II) was analogous to the sequence described above for the synthesis of compounds **9** and **10**.

Pharmacology

The cyprodime analogues were evaluated for opioid agonist and antagonist activity in the mouse vas deferens preparation (MVD).[1] Antagonist potencies at the three opioid receptor subtypes were determined against normorphine (NM; μ-selective agonist), ethylketocyclazocine (EKC, κ-selective agonist), and [D-Ala^2,D-Leu^5]enkephalin (DADLE, a mixed μ/δ agonist which is very δ selective in the MVD due to the high δ-receptor reserve in this preparation). All compounds were also tested for agonist activity in the guinea pig isolated ileum preparation (GPI),[1] a preparation particularly sensitive to κ agonists.

Agonist effects were designated as being due to predominantly μ-, κ-, or δ-receptor interactions on the basis of antagonism of the effect by the κ-selective antagonist norbinaltorphimine (3 nM),[10] the μ-selective antagonist cyprodime (1000 nM),[1] or the δ-selective antagonist naltrindole (10 nM).[11]

All compounds were tested up to a concentration of 50 μM. In the GPI, compounds which produced no inhibition of twitch height or produced an inhibition which was not antagonized by a combination of cyprodime (1000 nM) plus norbinaltorphimine (3 nM) were considered devoid of any opioid agonist (μ, κ) activity. Compounds producing dose–response effects only shifted by one of the antagonists were designated μ or κ agonists accordingly. None of the compounds possessed only μ-agonist activity.

Table II. Agonist Potencies in the GPI and MVD[a]

compd	cf. EKC[b] (κ) in GPI	cf. nM[c] (μ) in GPI	cf. DADLE[d] (δ) in MVD
4	0.0007[a]	NA[e]	0.001[a]
5	0.0008[a]	0.004	0.0004[a]
6	TS[f]	TS[f]	NA[e]
7	TS[f]	NA[e]	NA[e]
8	TS[f]	NA[e]	NA[e]
9	0.0014[a]	NA[e]	NA[e]
10	0.0004[a]	NA[e]	NA[e]
11	0.0015[a]	TS[f]	NA[e]
12	0.001[a]	1.0[a]	NA[e]

[a] Agonist potency is expressed as the ratio of the ED_{40} concentrations (i.e. the concentration producing 40% inhibition of twitch height) of the relevant agonist and the test compound. [b] EKC = ethylketocyclazocine. [c] NM = normorphine. [d] DADLE = [D-Ala^2,D-Leu^5]enkephalin. [e] NA = no agonist activity detected. [f] TS indicates a dose–response curve too shallow to estimate an ED_{40} (a 40% inhibition was not produced; for further explanations and a more detailed description of the procedures, see the Pharmacology section).

Compounds producing a dose–response effect that was shifted by cyprodime and further shifted by norbinaltorphimine (or vice versa) were designated as possessing both μ- and κ-agonist activity. An example of such a compound is **6**, which produced a shallow dose–response effect that was partially antagonized by norbinaltorphimine (leading to an even shallower curve) and totally antagonized by a combination of norbinaltorphimine and cyprodime. This is shown in Table II as possessing shallow dose–response curves at both μ and κ receptors. In contrast, compound **7** produced a shallow dose–response curve which was antagonized by norbinatorphimine but not further affected by the addition of cyprodime, indicating some κ but no detectable μ-agonist activity (see Table II).

In the MVD, compounds which produced no inhibition of twitch height or produced an inhibition which was not antagonized by naltrindole (10 nM) were considered devoid of any δ agonist activity.

The antagonist K_e values obtained are shown in Table I. Compounds **4** and **5** showed δ agonist effects in the MVD and consequently could not be tested for antagonist activity.

In the GPI only compounds **2**, **6a**, and **26** were pure antagonists. Compounds **7** and **8** produced very shallow κ dose–response curves. Compounds **9** and **10** produced only κ agonist effects, whereas compounds **6**, **11**, and **12**, produced both μ- and κ-agonist activity. In the case of compound **6**, the intrinsic activity was found to be very low (Table II).

In order to give some indication of the intrinsic activities of the partial agonists discussed in this paper, it should be noted that with the methodology described, the MVD will not normally detect any substantial agonism with buprenorphine or nalorphine. In the GPI, buprenorphine will produce marked agonist activity (40–80% depression) that is unaffected by norbinaltorphimine but blocked by cyprodime, whereas nalorphine produces a marked agonist effect (40–80% depression) that is unaffected by cyprodime but blocked by norbinaltorphimine. On the basis of these findings, compounds **7** and **8** are of lower intrinsic κ activity than nalorphine, whereas **9** and **10** were of similar intrinsic κ activity to nalorphine. Compound **6** had a lower μ intrinsic activity than buprenorphine and a lower κ intrinsic activity than nalorphine. Compounds **11** and **12** both possessed a combined μ- and κ-agonist activity suf-

(9) Olofson, R. A.; Marts, J. T.; Senet, J.-P.; Piteau, M.; Malfroot, Th. *J. Org. Chem.* **1984**, *49*, 2081.
(10) Portoghese, P. S.; Lipkowski, A. W.; Takemori, A. E. *J. Med. Chem.* **1987**, *30*, 238.
(11) Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E. *J. Med. Chem.* **1988**, *31*, 281.

ficient to produce a maximum depression in the GPI but negligible effects in the MVD. Compounds **4** and **5**, which were δ agonists in the MVD, both showed predominantly κ agonist activity in the GPI with intrinsic activity similar to that of nalorphine.

Discussion and Conclusion

From the biological results obtained with the present series of compounds, the following conclusions can be drawn concerning the effects of various changes to the cyprodime molecule.

Increasing the chain length at C-4 (compound **6a**) resulted in higher affinity for μ receptors (ca. 2-fold) but in very little change in either selectivity or intrinsic activity at any of the receptors. When increasing the size of the substituent at C-4 (compound **6**), μ affinity decreased while μ selectivity was retained. In this case very low intrinsic activity at μ and κ receptors was found. Decreasing the size of the substituent at C-4 (compound **4**) or removing it completely (compound **5**) resulted in an appreciable increase in intrinsic activity at κ, δ, and μ receptors. Compounds **4** and **5** both possess appreciable (albeit low potency) δ agonist effects in the MVD and κ (**4** and **5**) and μ (**5** only) agonist activity in the GPI. The agonist activity prevented the measurement of K_e values for these compounds.

Bridging the 4- and 5-positions with oxygen (compound **26**) resulted in a much lower μ/κ selectivity due to a 3-fold decrease in the μ affinity and a corresponding increase in the κ affinity. This compound possesses the lowest κ/μ ratio of all 12 compounds tested. As with cyprodime, this compound exhibits no significant agonist activity.

The introduction of a 3-OMe group (compound **7**) resulted in a marked decrease in the μ/δ selectivity due to small decrease in μ affinity and a large (ca. 10-fold) increase in δ affinity. The same effect is seen in the compounds **2** and **8**, and **10** and **12**. There is also an increase in intrinsic activity at μ and κ opioid receptors. Compound **7** showed appreciable κ agonist activity in the GPI, whereas cyprodime was a pure antagonist. Furthermore, compounds **11** and **12** both showed μ and κ agonist effects in the GPI, whereas compounds **9** and **10** possess no detectable μ agonist activity.

The replacement of the *N*-cyclopropylmethyl group with an *N*-allyl group (compound **2**) resulted in a decrease of μ/δ selectivity due to an approximately 4-fold decrease in μ affinity. The pairs of compounds **7** and **8**, **11** and **12**, and **9** and **10** show similar losses in μ/δ selectivity when the *N*-cyclopropylmethyl group is replaced by an *N*-allyl group.

Replacement of the 14-OMe group with a 14-OEt group (compound **9**) resulted in a slightly enhanced μ/κ selectivity due mainly to a ca. 2-fold increase in μ affinity in the MVD. However, this compound possesses substantial κ agonist activity in the GPI. A similar increase in κ agonist activity is seen with compounds **10–12**, which all possess a 14-OEt substituent.

In conclusion, introduction of a 4-*n*-butoxy substituent in position 4 resulted in a compound (**6a**) with higher affinity for μ opioid receptors but very little change in selectivity and intrinsic activity in comparison to those of cyprodime. All the other changes which were accomplished to the cyprodime molecule afforded compounds with either less μ-receptor affinity and less μ selectivity or increased agonist activity.

Experimental Section

Chemistry. Melting points were determined with a Kofler melting point microscope and are uncorrected. IR spectra were recorded on a Beckman Accu Lab 2 apparatus. ^{1}H NMR spectra were performed on a JEOL JNM-PMX 60 spectrometer or on a Bruker AM 300 spectrometer (300 MHz) and are reported in parts per million relative to tetramethylsilane as internal reference. Electron-ionization and chemical-ionization mass spectra (EI-MS and CI-MS, respectively) were obtained from a Finnigan MAT 44S apparatus. Optical rotations (concentration (g/100 mL), solvent) were determined with a Perkin-Elmer 141 polarimeter. Alumina basic (70–230 mesh ASTM) from Merck was used for column chromatography. Preparative-layer chromatography (PLC) was performed with plates from Merck (Kieselgel 60 F, 20 × 20 cm). Elemental analyses were performed at the Analytical Department of Hoffmann-La Roche & Co., Inc., Basle, Switzerland and at the Analytical Department of Reckitt & Colman, Kingston-upon-Hull, England.

(−)-*N*-Allyl-4,14-dimethoxymorphinan-6-one (2). A mixture of **3** (526 mg, 1.75 mmol), anhydrous K_2CO_3 (500 mg, 3.62 mmol), allyl bromide (0.16 mL, 1.9 mmol), and 6 mL of anhydrous DMF was stirred at 80 °C (bath temperature) for 30 min. After addition of 50 mL of H_2O and extractions with Et_2O (2 × 10 mL), the combined organic layers were washed with H_2O (2 × 10 mL) and brine, dried, and evaporated to give 380 mg of a crystalline residue, which was recrystallized from MeOH to yield 320 mg (54%) of **2**. A small portion of this material was recrystallized from MeOH for analysis: mp 143–146 °C; $[\alpha]^{20}_D$ = −113.7° (*c* 1.50, $CHCl_3$); IR (KBr) 1705 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15–6.60 (m, 3 arom H), 5.80 (m, 1 olef H), 5.28 (m, 2 olef H), 3.83 (s, 3 H, C-4 OCH_3), 3.25 (s, 3 H, C-14 OCH_3); EI-MS *m/z* 341 (M^+). Anal. ($C_{21}H_{27}NO_3$) C, H, N.

(−)-7,8-Didehydro-4,5α-epoxy-3-hydroxy-14-methoxy-*N*-methylmorphinan-6-one Hydrobromide (21·HBr). A solution of **20**[4] (5.0 g, 15.3 mmol) in 20 mL of 48% HBr was refluxed for 17 min and then evaporated. The gray, crystalline residue was treated with little MeOH to yield 4.5 g (75%) of **21**·HBr. A portion of this material was recrystallized from MeOH for analysis: mp >260 °C dec; $[\alpha]^{20}_D$ = −66.7° (*c* 0.91, DMF); IR (KBr) 3420 and 3130 (OH, $^+$NH), 1670 (CO) cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 9.30 (s, br, 2 H, OH, $^+$NH), 6.82 (d, 1 olef H, *J* = 10 Hz), 6.58 (s, 2 arom H), 6.35 (d, 1 olef H, *J* = 10 Hz), 5.08 (s, 1 H, C-5 H), 3.21 (s, 3 H, OCH_3), 2.90 (d, 3 H, $^+NCH_3$, *J* = 4 Hz). Anal. ($C_{18}H_{19}NO_4$·HBr·0.5MeOH) C, H, N, Br.

(−)-7,8-Didehydro-4,5α-epoxy-14-methoxy-*N*-methyl-3-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]morphinan-6-one (22). A mixture of **21**·HBr (8.0 g, 20.3 mmol), anhydrous K_2CO_3 (6.0 g, 43.4 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (3.8 g, 22.6 mmol), and 30 mL of anhydrous DMF was stirred at room temperature under N_2 for 20 h. After addition of 300 mL of H_2O and extraction with CH_2Cl_2 (2 × 80 mL), the combined organic layers were washed with H_2O (3 × 200 mL) and brine, dried, and evaporated to give 9.2 g of a slightly brown, crystalline residue, which was recrystallized from EtOH to yield 8.53 g (92%) of **22**: mp 187–189 °C; $[\alpha]^{22}_D$ = −86.7° (*c* 0.82, $CHCl_3$); IR (KBr) 3400 (OH), 1670 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.95–7.50 (m, 5 arom H), 7.24 (d, 1 arom H, *J* = 8 Hz), 6.81 (d, 1 olef H, *J* = 10 Hz), 6.76 (d, 1 arom H, *J* = 8 Hz), 6.35 (d, 1 olef H, *J* = 10 Hz), 4.82 (s, 1 H, C-5 H), 3.31 (s, 3 H, OCH_3), 2.50 (s, 3 H, NCH_3). Anal. ($C_{25}H_{23}N_5O_4$) C, H, N.

(−)-4,5α-Epoxy-14-methoxy-*N*-methylmorphinan-6-one (23). Ten percent Pd/C catalyst (21.3 g) was added to a solution of **22** (3.0 g, 6.6 mmol) in 60 mL of glacial AcOH. This mixture was hydrogenated at 50 psi and 40 °C for 16 h. The catalyst was filtered off; the filtrate was evaporated, alkalized with concentrated NH_4OH, and extracted with CH_2Cl_2 (2 × 40 mL); and the combined organic layers were dried and evaporated to yield 1.93 g of a slightly yellow, crystalline residue, which was treated with MeOH to give 1.54 g (78%) of **23**: mp 170–173 °C (lit.[3] mp 172–174 °C). This material proved to be identical with an authentic sample by mixed melting point, IR, and ^{1}H NMR.

(−)-4,5α-Epoxy-14-methoxy-*N*-[(2,2,2-trichloroethoxy)carbonyl]morphinan-6-one (24). 2,2,2-Trichloroethyl chloroformate (40 mL, 284 mmol) was added dropwise to a refluxing mixture of **23** (15 g, 50.1 mmol), anhydrous $KHCO_3$ (20 g, 200 mmol), and 110 mL of EtOH-free $CHCl_3$ during a period of 45 min. The resulting mixture was stirred under reflux for 8 h. The inorganic solid was filtered off and washed with EtOH-free $CHCl_3$, and the filtrate was evaporated at 90 °C (bath temperature), first at 10 Torr, then at 1 Torr, to afford a semicrystalline solid, which was treated with boiling isopropyl ether to give 22.8 g of crystalline

material. Recrystallization from 40 mL of EtOH yielded 20.74 g (90%) of **24**. A small portion was recrystallized from MeOH to give an analytical sample: mp 159–161 °C; ^{1}H NMR ($CDCl_3$) δ 7.12–6.62 (m, 3 H, arom H), 4.77 (s, 2 H, OCH_2), 4.59 (s, 1 H, C-5 H), 3.30 (3 H, OCH_3); CI-MS ($^+NH_4$) *m/z* 477 (M^+ + 18). Anal. ($C_{20}H_{20}Cl_3NO_5$) C, H, N.

(−)-4,5α-Epoxy-14-methoxymorphinan-6-one Hydrobromide (25·HBr). Activated Zn powder (10 g, 153 mmol) was added in portions to a cooled (−10 °C) solution of **24** (20 h, 43.4 mmol) in 200 mL of 80% AcOH within 5 min with stirring. After 30 min, more Zn powder (5 g, 76 mmol) was added. The resulting mixture was stirred at −10 to −5 °C for 4 h. After filtration, the filtrate was diluted with 300 mL of H_2O, washed with Et_2O (2 × 200 mL), rendered alkaline with concentrated NH_4OH, and extracted with $CHCl_3$ (3 × 150 mL). The combined organic layers were dried and evaporated to give 8.2 g (66%) of **25** as colorless, crystalline solid (mp 182–190 °C). For analysis the HBr salt (**25**·HBr) was formed in the usual way: mp 294–298 °C dec (acetone); ^{1}H NMR (Me_2SO-d_6) δ 8.73 (s, br, 2 H, $^+NH_2$), 7.22–6.62 (m, 3 H, arom H), 4.93 (s, 1 H, C-5 H), 2.35 (s, 3 H, OCH_3); CI-MS *m/z* 286 (M^+ + 1). Anal. ($C_{17}H_{19}NO_3$·HBr) C, H, N, Br.

(−)-*N*-(Cyclopropylmethyl)-4,5α-epoxy-14-methoxymorphinan-6-one (26). A mixture of **25**·HBr (1.15 g, 3.14 mmol), K_2CO_3 (2 g, 15.6 mmol), cyclopropylmethyl chloride (0.41 mL, 4.43 mmol), and 15 mL anhydrous DMF was stirred at 90 °C (bath temperature) for 6 h. The inorganic solid was filtered off and the filtrate was evaporated. The oily residue was partitioned between CH_2Cl_2 and H_2O; the organic layer was dried and evaporated to afford 1.05 g of a slightly brown oil, which was crystallized from 2-propanol to yield 825 mg (77%) of **26**. An analytical sample was recrystallized from 2-propanol: mp 140–142 °C; $[\alpha]^{20}_D$ = −282.9° (*c* 0.84, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.16–6.57 (m, 3 H, arom H), 4.58 (s, 1 H, C-5 H), 3.32 (s, 3 H, OCH_3); EI-MS *m/z* 359 (M^+). Anal. ($C_{21}H_{25}NO_3$·0.2 2-propanol) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-4-hydroxy-14-methoxymorphinan-6-one (4). Activated Zn powder (3.2 g, 48.9 mmol) was added to a refluxing mixture of **26** (1.57 g, 4.63 mmol), NH_4Cl (3.2 g, 59 mmol), and 40 mL of MeOH within 5 min. This mixture was stirred and refluxed for another 30 min, cooled, and filtered, and the filtrate was evaporated. Alkalization with concentrated NH_4OH was followed by extraction with $CHCl_3$/MeOH (3:1). The organic layer was dried and evaporated to give 1.56 g of a slightly brown foam, which was crystallized from MeOH to yield 1.12 g (71%) of **4**. A small portion was recrystallized from MeOH to afford an analytical sample: mp 188–191 °C dec; $[\alpha]^{20}_D$ = −164.9° (*c* 0.73, CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ 7.03–6.40 (m, 3 arom H), 3.35 (s, 3 H, OCH3); EI-MS *m/z* 341 (M^+). Anal. ($C_{21}H_{27}NO_3$·0.5MeOH) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-4,14-dimethoxymorphinan-6-one Hydrobromide (Cyprodime Hydrobromide; 1·HBr). A mixture of K_2CO_3 (400 mg, 3.1 mmol) and 15 mL of anhydrous DMF was gassed at room temperature with N_2 for 30 min. Then **4** (285 mg, 0.83 mmol) and phenyltrimethylammonium chloride (440 mg, 2.56 mmol) were added, and the resulting mixture was stirred under N_2 at 80 °C (bath temperature) for 4.5 h. The inorganic material was filtered off and the filtrate was evaporated. The oily residue was dissolved in diluted AcOH and the pH was adjusted to 6–6.5 with concentrated NH_4OH. The residue was then washed with cyclohexane (2 × 10 mL), rendered alkaline with concentrated NH_4OH, and extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were washed with brine, dried, and evaporated to yield 220 mg of a slightly brown, crystalline solid, which was recrystallized from MeOH to afford 185 mg (62%) of **1** as colorless crystals (mp 155–159 °C). The base was converted into the HBr salt (1·HBr) in the usual way. It was identical by mixed melting point, TLC, IR, and ^{1}H NMR with authentic material.[1]

(−)-*N*-(Cyclopropylmethyl)-14-methoxy-4-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]morphinan-6-one (27). A mixture of **4** (500 mg, 1.46 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (285 mg, 1.58 mmol), K_2CO_3 (700 mg, 5.07 mmol), and 5 mL of anhydrous DMF was stirred under N_2 at room temperature for 24 h. After addition of 50 mL of H_2O and extraction with AcOEt (2 × 30 mL), the combined organic layers were washed with H_2O (3 × 30 mL) and brine, dried, and evaporated to yield 680 mg of a crystalline residue, which was treated with boiling MeOH to give 590 mg (83%) of pure **27**: mp 188–189 °C; ^{1}H NMR ($CDCl_3$) δ 8.15–6.90 (m, 8 arom H) 3.32 (s, 3 H, OCH3); EI-MS *m/z* 485 (M^+). Anal. ($C_{28}H_{31}N_5O_3$) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-14-methoxymorphinan-6-one Salicylate (5·Salicylic Acid). A mixture of **27** (330 mg, 0.68 mmol), 10% Pd/C (300 mg), and 50 mL of glacial AcOH was hydrogenated at 35 °C and 40 psi for 21 h. The catalyst was filtered off and the filtrate was evaporated. The residue was alkalized with concentrated NH_4OH and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic layers were washed with brine, dried, and evaporated to give 205 mg of a yellow oil, which was chromatographed on alumina basic grade III (length of the column 23 cm, diameter 1.3 cm, elution with CH_2Cl_2) to yield 155 mg (73%) of pure **5** as a colorless oil. The salicylate (**5**·salicylic acid) (205 mg) was prepared in the usual way: mp 151–153 °C (MeOH/Et_2O); $[\alpha]^{20}_D$ = −83.8° (*c* 1.02, $CHCl_3$); IR (KBr) 3400 (OH, ^+NH), 1710 (CO) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 9.30 (s, 2 H, OH, ^+NH), 7.94–6.57 (m, 8 arom H), 3.38 (s, 3 H, OCH_3); EI-MS *m/z* 325 (M^+). Anal. ($C_{21}H_{27}NO_2$·C_7H_6O·0.5MeOH) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-4-(isopropyloxy)-14-methoxymorphinan-6-one (6). NaH (89 mg, 3.7 mmol; obtained from 160 mg of a 55% NaH dispersion in oil by washings with petroleum ether) was added to a solution of **4** (420 mg, 1.23 mmol) in 2 mL of anhydrous DMF under N_2 at 5 °C (bath temperature) with stirring. After 10 min, isopropyl bromide (450 mg, 3.66 mmol) was added and the resulting mixture was stirred at room temperature for 70 h. Excess NaH was destroyed carefully by addition of small pieces of ice, and the mixture was poured on 10 mL of H_2O and extracted with Et_2O (2 × 10 mL). The combined organic layers were washed with H_2O (3 × 10 mL) and brine, dried, and evaporated to yield 320 mg of a slightly yellow foam, which was crystallized from MeOH to give 60 mg of **6**. The mother liquor was evaporated and chromatographed on alumina basic grade II (length of the column 15 cm, diameter 2.5 cm, elution with CH_2Cl_2) to afford 136 mg of a colorless foam which was crystallized from MeOH to yield another 92 mg of **6**: total yield 152 mg (32%); mp 98–100 °C; $[\alpha]^{20}_D$ = −84.2° (*c* 0.77, CH_2Cl_2); IR (KBr) 1700 (CO) cm^{-1}; ^{1}H NMR (300 MHz; $CHCl_3$) δ 7.03 (t, 1 arom H, *J* = 8 Hz), 6.65 (d, 1 arom H, *J* = 8 Hz), 6.60 (d, 1 arom H, *J* = 8 Hz), 4.58 (sept., 1 H, CHO, *J* = 7 Hz), 3.37 (s, 3 H, CH_3O), 1.46 (d, 3 H, CH_3, *J* = 7 Hz), 1.34 (d, 3 H, CH_3, *J* = 7 Hz); CI-MS *m/z* 384 (M^+ + 1). Anal. ($C_{24}H_{33}NO_3$) C, H, N.

(−)-4-*n*-Butoxy-14-methoxy-*N*-methylmorphinan-6-one (14). NaH (166 mg, 6.9 mmol; from 302 mg of a 55% NaH dispersion in oil, obtained by washings with petroleum ether) was added to a solution of **13** (700 mg, 2.3 mmol) in 5 mL of anhydrous DMF under N_2 at 5 °C (bath temperature) with stirring. After 15 min, n-C_4H_9I (550 mg, 3.0 mmol) was added and the resulting mixture was stirred at 5 °C (bath temperature) for 3 h. Excess NaH was destroyed carefully by addition of small pieces of ice, the reaction mixture was poured on 20 mL of H_2O and extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with H_2O (3 × 20 mL) and brine, dried, and evaporated to give 735 mg of a slightly brown oil, which was crystallized from MeOH to yield 380 mg (54%) of **14** (mp 123–127 °C). A portion was recrystallized from MeOH for analysis: mp 126–127 °C; $[\alpha]^{20}_D$ = −32.6° (*c* 0.61, $CHCl_3$); ^{1}H NMR (300 MHz; $CDCl_3$) δ 7.05 (t, 1 arom H, *J* = 8 Hz), 6.67 (d, 2 arom H, *J* = 8 Hz), 3.34 (s, 3 H, OCH_3), 2.40 (s, 3 H, NCH_3), 1.01 (t, 3 H, CH_3, *J* = 7 Hz). Anal. ($C_{22}H_{31}NO_3$) C, H, N.

(−)-4-*n*-Butoxy-*N*-(cyclopropylmethyl)-14-methoxymorphinan-6-one (6a). A mixture of **14** (270 mg, 0.76 mmol), $NaHCO_3$ (755 mg, 9.0 mmol), 1-chloroethyl chloroformate (1.3 g, 9.1 mmol), and 10 mL of $ClCH_2CH_2Cl$ was stirred at 60–65 °C (bath temperature) for 2 h. The inorganic solid was filtered off, the filtrate was evaporated, and the residue (**15**) was refluxed for 30 min in 10 mL of MeOH. After evaporation, the oily residue was alkalized with concentrated NH_4OH, extracted with CH_2Cl_2, dried, and evaporated to give 255 mg of **16** as slightly pink, crystalline residue (mp 112–116 °C; CI-MS *m/z* 344 (M^+ + 1)), which was not further purified. Anhydrous K_2CO_3 (300 mg, 2.2 mmol) and cyclopropylmethyl chloride (75 mg, 0.83 mmol) were added to a solution of this material in 10 mL of anhydrous DMF. This mixture was stirred at 80–85 °C for 4 h and then cooled, 20 mL of H_2O was added, and the mixture was extracted with Et_2O (3 × 10 mL). The combined organic layers were washed with H_2O

(3 × 10 mL), dried, and evaporated to give 280 mg of a slightly red oil, which was crystallized from MeOH to yield 167 mg (56%) of **6** (mp 107–112 °C). For analysis a portion of this material was recrystallized from MeOH: mp 110–114 °C; $[\alpha]^{20}_D$ = −74.9° (*c* 0.63, $CHCl_3$); IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.04 (t, 1 arom H, *J* = 8 Hz), 6.65 (m, 2 arom H), 3.42 (s, 3 H, OCH_3), 1.00 (t, 3 H, CH_3, *J* = 7 Hz); CI–MS *m/z* 398 (M^+ + 1). Anal. ($C_{25}H_{35}NO_3$) C, H, N.

(−)-3,4,14-Trimethoxymorphinan-6-one Oxalate (19·Oxalic Acid). 2,2,2-Trichloroethyl chloroformate (24 mL, 172 mmol) was added dropwise to a refluxing mixture of **17** (7.3 g, 21.1 mmol), anhydrous $KHCO_3$ (18.3 g, 183 mmol), and 200 mL of EtOH-free $CHCl_3$ under N_2 during a period of 15 min. This mixture was stirred under reflux for an additional 1.5 h and filtered, and the filtrate was evaporated at 90 °C (bath temperature), first at 10 Torr, then at 1 Torr. The resulting residue [10.6 g of **18** as a glassy solid: IR ($CHCl_3$) 1775 (carbamate), 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.68 (s, 2 arom H), 4.80 (m, 2 H, OCH_2), 3.88 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 3.31 (s, 3 H, C-14 OCH_3)] was used for the next step without further purification. Activated Zn powder (20 g, 306 mmol) was added in portions to a refluxing mixture of **18** (10.5 g), NH_4Cl (20 g, 369 mmol), and 200 mL of MeOH within 5 min. This mixture was stirred under reflux for an additional 30 min, cooled, and filtered, and the filtrate was evaporated. The oily residue was partitioned between 400 mL of 1 N NaOH and 100 mL of $CHCl_3$; the organic layer washed with brine, dried, and evaporated to yield 5.9 g of a slightly brown oil, which was converted into the oxalate (**19**·oxalic acid; 4.3 g, 52%) in the usual way. An analytical sample was obtained by recrystallization of a portion of this material from acetone: mp 138–142 °C; $[\alpha]^{20}_D$ = −110.3° (*c* 0.76, 95% EtOH); IR (KBr) 3420 (OH, $^+NH_2$), 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.80 (s, br, 3 H, OH, $^+NH_2$), 6.62 (d × d, 2 arom H, *J* = 8, 8 Hz), 3.87 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.34 (s, 3 H, C-14 OCH_3); EI–MS *m/z* 331 (M^+). Anal. ($C_{19}H_{25}NO_4 \cdot C_2H_4O_4$) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-3,4,14-trimethoxymorphinan-6-one Salicylate (7·Salicylic Acid). A mixture of **19**·oxalic acid (2.5 g, 5.93 mmol), K_2CO_3 (4 g, 28.94 mmol), cyclopropylmethyl chloride (0.66 mL, 7.2 mmol), and 15 mL of anhydrous DMF was stirred under N_2 at 100 °C (bath temperature) for 20 h. After addition of 150 mL of ice/water, the mixture was extracted with Et_2O (2 × 35 mL), and the combined Et_2O phases were washed with H_2O (4 × 20 mL), dried, and evaporated to give 1.75 g of a brown oil. This oil was chromatographed on alumina basic grade II (length of the column 12.5 cm, diameter 3.5 cm, elution with CH_2Cl_2) to yield 1.56 g of a colorless oil, which was converted into the salicylate (**7**·salicylic acid; 1.6 g, 52%) in the usual way. An analytical sample was obtained by recrystallization from MeOH/Et_2O: mp 158–159 °C; $[\alpha]^{20}_D$ = −63.4° (*c* 0.93, $CHCl_3$); IR (KBr) 3420 (OH, ^+NH), 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 12.22 (s, 2 H, OH, ^+NH), 7.97–6.60 (m, 6 arom H), 3.92 (s, 3 H, OCH_3), 3.80 (s, 3 H, OCH_3), 3.46 (s, 3 H, C-14 OCH_3); EI–MS *m/z* 385 (M^+). Anal. ($C_{23}H_{31}NO_4 \cdot C_7H_6O_3$) C, H, N.

(−)-*N*-Allyl-3,4,14-trimethoxymorphinan-6-one Hydrobromide (8·HBr). A mixture of **19**·oxalic acid (1.3 g, 3.08 mmol), K_2CO_3 (1.5 g, 10.6 mmol), allyl bromide (0.35 mL, 4.04 mmol), and 30 mL of anhydrous DMF was stirred at 80 °C (bath temperature) for 30 min. The inorganic material was filtered off, the filtrate was evaporated, the oily residue was partitioned between Et_2O and H_2O, and the organic layer was dried and evaporated to yield 1.05 g of **8** as a colorless oil, which was converted into the HBr salt (**8**·HBr; 1.15 g, 82%) in the usual way. A portion of this material was recrystallized from acetone to give an analytical sample: mp 233–236 °C dec; $[\alpha]^{20}_D$ = −31.0° (*c* 1.38, 95% EtOH); IR (KBr) 3600 and 3400 (OH, ^+NH), 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 10.10 (s, br, OH, ^+NH), 6.75 (s, 2 arom H), 6.12 (m, 1 olef H), 5.60 (m, 2 olef H), 3.92 (s, 3 H, OCH_3), 3.79 (s, 3 H, OCH_3), 3.47 (s, 3 H, C-14 OCH_3); EI–MS *m/z* 371 (M^+). Anal. ($C_{22}H_{29}NO_4 \cdot HBr \cdot H_2O$) C, H, N.

(−)-7,8-Didehydro-4,5α-epoxy-14-ethoxy-3-hydroxy-*N*-methylmorphinan-6-one Hydrobromide (29·HBr). A solution of **28**[4] (31.8 g, 93.1 mmol) in 150 mL of 48% HBr was refluxed for 20 min. After evaporation, a gray foam was obtained, which was crystallized from MeOH/Et_2O to give 20.7 g (54%) of **10**·HBr. For analysis a small portion was recrystallized from MeOH: mp 233–237 °C dec; $[\alpha]^{20}_D$ = −46.5° (*c* 1.04, MeOH); IR (KBr) 3420 and 3200 (OH, ^+NH), 1680 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.60 and 9.20 (2 s, br, OH, ^+NH); 6.97 (d, 1 olef H, *J* = 10 Hz), 6.73 (s, 2 arom H), 6.39 (d, 1 olef H, *J* = 10 Hz), 5.16 (s, 1 H, C-5 H), 3.03 (s, 3 H, $^+NCH_3$), 1.21 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{19}H_{21}NO_4$·HBr) C, H, N.

(−)-7,8-Didehydro-4,5α-epoxy-14-ethoxy-*N*-methyl-3-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]morphinan-6-one (30). A mixture of **29**·HBr (20 g, 49.0 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (9.52 g, 52.7 mmol), anhydrous K_2CO_3 (14.05 g, 101.6 mmol), and 95 mL of anhydrous DMF was stirred at room temperature for 38 h. The inorganic solid was filtered off, the filtrate was evaporated, and the oily residue was dissolved in 200 mL of CH_2Cl_2, washed with H_2O (3 × 200 mL), dried, and evaporated to give 25.5 g of a brown oil, which was crystallized from EtOH to yield 20.25 g (88%) of **30** (mp 191–198 °C). A portion of this material was recrystallized twice from MeCN for analysis: mp 203–205 °C; $[\alpha]^{20}_D$ = −78.8° (*c* 0.92, $CHCl_3$); IR (KBr) 1680 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90–7.35 (m, 5 arom H), 7.08 (d, 1 arom H, *J* = 8 Hz), 6.73 (d, 1 olef H, *J* = 10 Hz), 6.64 (d, 1 arom H, *J* = 8 Hz), 6.13 (d, 1 olef H, *J* = 10 Hz), 4.72 (s, 1 H, C-5 H), 2.41 (s, 3 H, NCH_3), 1.14 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{26}H_{25}N_5O_4$) C, H, N.

(−)-4,5α-Epoxy-14-ethoxy-*N*-methylmorphinan-6-one (31). Ten grams of 10% Pd/C catalyst was added to a solution of **30** (20.2 g, 42.8 mmol) in 200 mL of glacial AcOH. This mixture was hydrogenated at 40 °C and 50 psi for 16 h. The catalyst was filtered off, the filtrate was evaporated, and the residue was alkalized with concentrated NH_4OH and extracted with CH_2Cl_2 (2 × 400 mL). The combined organic layers were washed with H_2O (1 L) and brine, dried, and evaporated to give 15.44 g of a red-brown oil, which was crystallized from 13 mL of MeOH to yield 8.9 g (66%) of **31** (mp 160–168 °C). An analytical sample was obtained by recrystallization from MeOH: mp 170–171 °C; $[\alpha]^{20}_D$ = −254.6° (*c* 1.07, $CHCl_3$); IR (KBr) 1715 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02–6.50 (m, 3 arom H), 4.54 (s, 1 H, C-5 H), 2.35 (s, 3 H, NCH_3), 1.26 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

(−)-14-Ethoxy-4-hydroxy-*N*-methylmorphinan-6-one (32). Activated Zn powder (17.6 g, 269 mmol) was added to a refluxing mixture of **31** (8.8 g, 28.1 mmol), NH_4Cl (17.6 g, 329 mmol), and 150 mL of MeOH within 5 min. After stirring and refluxing for an additional 30 min, the mixture was filtered, the filtrate was evaporated, and the residue was alkalized with concentrated NH_4OH and extracted with $CHCl_3$/MeOH (3:1) (2 × 300 mL). The combined organic layers were dried and evaporated to yield 4.0 g of a slightly pink, crystalline solid, which was recrystallized from 10 mL of MeOH to give 2.77 g (31%) of **32**. For analysis a small portion was recrystallized from MeOH: mp 228–230 °C; $[\alpha]^{20}_D$ = −66.6° (*c* 1.08, $CHCl_3$); IR (KBr) 3200 (OH), 1700 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.20 (s, br, 1 H, OH), 7.00–6.50 (m, 3 arom H), 2.24 (s, 3 H, NCH_3), 1.20 (t, 3 H, *J* = 6 Hz). Anal. ($C_{19}H_{25}NO_3 \cdot 0.2MeOH$) C, H, N.

(−)-14-Ethoxy-4-methoxy-*N*-methylmorphinan-6-one (33). A mixture of **32** (3.0 g, 9.5 mmol), K_2CO_3 (4.0 g, 28.9 mmol), phenyltrimethylammonium chloride (3.27 g, 19.0 mmol), and 50 mL of anhydrous DMF was stirred at 80 °C (bath temperature) for 4 h. The inorganic material was filtered off, the filtrate was evaporated, and the oily residue was dissolved in CH_2Cl_2 (70 mL), washed with H_2O (3 × 50 mL), dried, and evaporated to give 2.7 g of a slightly brown, crystalline residue, which was treated with MeOH to yield 2.26 g (72%) of slightly yellow **33**. An analytical sample was obtained by recrystallization of a small sample from MeOH/H_2O (1:1): mp 128–130 °C; $[\alpha]^{20}_D$ = −68.6° (*c* 0.84, $CHCl_3$); IR (KBr) 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.08–6.60 (m, 3 arom H), 3.81 (s, 3 H, OCH_3), 2.32 (s, 3 H, NCH_3), 1.27 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{20}H_{27}NO_3$) C, H, N.

(−)-14-Ethoxy-4-methoxymorphinan-6-one Hydrochloride (35·HCl). A mixture of **33** (2.0 g, 6.1 mmol), $NaHCO_3$ (2.56 g, 30.5 mmol), 1-chloroethyl chloroformate (3.32 mL, 30.5 mmol), and 25 mL of $ClCH_2CH_2Cl$ was stirred at 60–65 °C (bath temperature) for 5.5 h. After filtration, the filtrate was evaporated to give 2.4 g of **34** as crystalline solid, which was not further purified and characterized. This solid was dissolved in 30 mL of MeOH, the solution was refluxed for 30 min and filtered, and the filtrate was evaporated. The residue (2.25 g of a slightly brown foam) was crystallized from MeOH (2 mL) to yield 1.96 g (92%)

of **35**·HCl. For analysis a small portion was recrystallized from MeOH/Et_2O: mp >250 °C dec; $[\alpha]^{20}_D$ = −32.7° (*c* 1.16, MeOH); IR (KBr) 3280 ($^+NH_2$), 1710 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.20 (s, br, 2 H, $^+NH_2$), 7.33–6.62 (m, 3 arom H), 3.84 (s, 3 H, OCH_3), 1.37 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{19}H_{25}NO_3$·HCl·MeOH) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-14-ethoxy-4-methoxymorphinan-6-one (9). A mixture of **35**·HCl (900 mg, 2.5 mmol), anhydrous K_2CO_3 (900 mg, 6.5 mmol), cyclopropylmethyl chloride (0.27 mL, 2.9 mmol), and 7 mL of anhydrous DMF was stirred at 100 °C (bath temperature) for 21 h. After addition of 100 mL of H_2O, the mixture was extracted with Et_2O (3 × 30 mL); the combined organic layers were washed with H_2O (2 × 100 mL), dried, and evaporated to give 890 mg of a slightly brown oil, which was crystallized from MeOH to yield 530 mg (56%) of **9** (mp 108–111 °C). A portion of this material was further purified with PLC (mobile phase: $CHCl_3$/MeOH/NH_4OH 90/9/1; elution with MeOH) to give an analytical sample: mp 111–112 °C; $[\alpha]^{20}_D$ = −109.5° (*c* 0.99, $CHCl_3$); IR (KBr) 1705 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.20–6.58 (m, 3 arom H), 3.82 (s, 3 H, OCH_3), 1.28 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{23}H_{31}NO_3$·0.5MeOH) C, H, N.

(−)-*N*-Allyl-14-ethoxy-4-methoxymorphinan-6-one (10). A mixture of **35**·HCl (700 mg, 2.00 mmol), anhydrous K_2CO_3 (700 mg, 5.0 mmol), allyl bromide (0.18 mL, 2.1 mmol), and 5 mL of anhydrous DMF was stirred at room temperature for 24 h. After addition of 50 mL of H_2O, the mixture was extracted with Et_2O (3 × 30 mL); the combined organic layers were washed with H_2O (2 × 100 mL), dried, and evaporated. The residue (630 mg of a colorless, crystalline solid) was recrystallized from MeOH to yield 500 mg (71%) of **10**: mp 93–95 °C; $[\alpha]^{20}_D$ = −101.4° (*c* 1.04, $CHCl_3$); IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.07–6.55 (m, 3 arom H), 5.80 (m, 1 olef H), 5.18 (m, 2 olef H), 3.80 (s, 3 H, OCH_3), 1.26 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{22}H_{29}NO_3$·0.8MeOH) C, H, N.

(−)-14-Ethoxy-4-hydroxy-3-methoxy-*N*-methylmorphinan-6-one (37). Activated Zn powder (13 g, 199 mmol) was added in small portions to a refluxing mixture of **36** (6.5 g, 18.9 mmol), NH_4Cl (13 g, 243 mmol), and 100 mL of MeOH within 5 min with stirring. After stirring and refluxing for an additional 30 min, the solid was filtered off, the filtrate was evaporated, and the residue was alkalized with concentrated NH_4OH and extracted with $CHCl_3$/MeOH (3:1) (2 × 200 mL). The combined organic layers were dried and evaporated to give 5.93 g of a colorless oil, which was crystallized from MeOH to yield 3.06 g (47%) of **37**. An analytical sample was obtained by recrystallization of a small portion: mp 210–212 °C; $[\alpha]^{20}_D$ = −77.6° (*c* 1.09, $CHCl_3$); IR (KBr) 3480 (OH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (d, 1 arom H, *J* = 8 Hz), 6.61 (d, 1 arom H, *J* = 8 Hz), 3.85 (s, 3 H, OCH_3), 2.36 (s, 3 H, NCH_3), 1.27 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{20}H_{27}NO_4$) C, H, N.

(−)-3,4-Dimethoxy-14-ethoxy-*N*-methylmorphinan-6-one (38). A mixture of **37** (3.0 g, 8.7 mmol), anhydrous K_2CO_3 (4 g, 28.9 mmol), phenyltrimethylammonium chloride (3.17 g, 18.4 mmol), and 30 mL of anhydrous DMF was stirred at 80 °C (bath temperature) for 8 h. After filtration, the filtrate was evaporated, and the oily residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (3 × 40 mL), dried, and evaporated to yield 3.05 g of a brownish, semicrystalline residue, which was crystallized from MeOH to give 2.31 g (71%) of **38**. Recrystallization of a portion of this material from MeOH yielded an analytical sample: mp 112–114 °C $[\alpha]^{20}_D$ = −75.7° (*c* 0.86, $CHCl_3$); IR (KBr) 3480 (OH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.67 (s, 2 arom H), 3.89 (s, 3 H, OCH_3), 3.76 (s, 3 H, OCH_3), 2.30 (s, 3 H, NCH_3), 1.25 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{21}H_{29}NO_4$·0.5MeOH) C, H, N.

(−)-3,4-Dimethoxy-14-ethoxymorphinan-6-one (40). A mixture of **38** (1.75 g, 4.7 mmol), $NaHCO_3$ (2.2 g, 26.2 mmol), 1-chloroethyl chloroformate (2.85 mL, 26.2 mmol), and 20 mL of $ClCH_2CH_2Cl$ was stirred at 60–65 °C (bath temperature) for 6 h. After filtration, the filtrate was evaporated to give 2.04 g of **39** as colorless oil, which was not further purified and characterized. This oil was dissolved in 30 mL MeOH, the solution was refluxed for 30 min and filtered, and the filtrate was evaporated. The reddish oily residue (1.78 g) was alkalized with concentrated NH_4OH and extracted with CH_2Cl_2 (2 × 30 mL); the combined organic layers were washed with brine, dried, and evaporated to give 1.52 g of an oil, which was crystallized from MeOH to yield 1.17 g (70%) of **40**. An analytical sample was obtained by recrystallization of a small sample from MeOH: mp 133–136 °C; $[\alpha]^{20}_D$ = −50.0° (*c* 0.96, $CHCl_3$); IR (KBr) 3440 (NH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.65 (s, 2 arom H), 3.88 (s, 3 H, OCH_3), 3.73 (s, 3 H, OCH_3), 1.28 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{20}H_{27}NO_4$·0.5MeOH) C, H, N.

(−)-*N*-(Cyclopropylmethyl)-3,4-dimethoxy-14-ethoxymorphinan-6-one (11). A mixture of **40** (860 mg, 2.38 mmol), anhydrous K_2CO_3 (860 mg, 6.2 mmol), cyclopropylmethyl chloride (0.25 mL, 2.7 mmol), and 8 mL of anhydrous DMF was stirred at 100 °C (bath temperature) for 20 h. After addition of 100 mL of H_2O, the mixture was extracted with Et_2O (3 × 30 mL), and the combined organic layers were washed with H_2O (2 × 60 mL), dried, and evaporated to yield 860 mg of a brown oil, which was crystallized from MeOH to give 515 mg (53%) of **11**. Recrystallization from MeOH gave an analytical sample: mp 128–130 °C; $[\alpha]^{20}_D$ = −110.6° (*c* 0.94, $CHCl_3$); IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (s, 2 arom. H), 3.91 (s, 3 H, OCH_3), 3.78 (s, 3 H, OCH_3), 1.28 (t, 3 H, CH_3, *J* = 6 Hz); CI–MS *m*/*z* 400 (M^+ + 1). Anal. ($C_{24}H_{33}NO_4$) C, H, N.

(−)-*N*-Allyl-3,4-dimethoxy-14-ethoxymorphinan-6-one Hydrobromide (12·HBr). A mixture of **40** (550 mg, 1.52 mmol), anhydrous K_2CO_3 (550 mg, 4.0 mmol), allyl bromide (0.14 mL, 1.63 mmol), and 6 mL of anhydrous DMF was stirred at room temperature for 22 h. After addition of 30 mL of H_2O, the mixture was extracted with Et_2O (3 × 20 mL), and the combined organic layers were washed with H_2O (2 × 50 mL), dried, and evaporated to give 565 mg of a colorless oil, which was converted into the HBr salt (**12**·HBr) in the usual way (crystallized from acetone; 477 mg, 65%). An analytical sample was obtained by recrystallization from MeOH: mp 234–238 °C dec; $[\alpha]^{20}_D$ = −65.5° (*c* 0.99, $CHCl_3$); IR (KBr) 3440 (^+NH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.78 (s, 2 arom H), 6.07 (m, 1 olef H), 5.62 (m, 2 olef H), 3.91 (s, 3 H, OCH_3), 3.77 (s, 3 H, OCH_3), 1.51 (t, 3 H, CH_3, *J* = 6 Hz). Anal. ($C_{23}H_{31}NO_4$·HBr·0.5MeOH) C, H, N.

Pharmacology. For materials and methods, see ref 1.

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Registry No. 1, 118111-54-9; 1·HBr, 118111-51-6; **2**, 124919-19-3; **3**, 118111-53-8; **4**, 124919-20-6; **5**, 124919-21-7; **5**·salicylic acid, 124919-22-8; **6**, 124919-23-9; **6a**, 124919-53-5; **7**, 124919-24-0; **7**·salicylic acid, 124919-25-1; **8**, 124919-55-7; **8**·HBr, 124919-26-2; **9**, 124919-27-3; **10**, 124919-28-4; **11**, 124919-29-5; **12**, 124919-56-8; **12**·HBr, 124919-30-8; **13**, 92055-58-8; **14**, 124919-31-9; **15**, 124919-32-0; **16**, 124919-33-1; **17**, 92055-62-4; **18**, 124919-34-2; **19**, 124919-35-3; **19**·oxalic acid, 124919-36-4; **20**, 38252-24-3; **21**·HBr, 124942-33-2; **22**, 124919-37-5; **23**, 92055-57-7; **24**, 124919-38-6; **25**, 124919-54-6; **25**·HBr, 124919-39-7; **26**, 124919-40-0; **27**, 124919-41-1; **28**, 79823-86-2; **29**·HBr, 124919-42-2; **30**, 124919-43-3; **31**, 124919-44-4; **32**, 124919-45-5; **33**, 124919-46-6; **34**, 124919-47-7; **35**·HCl, 124919-48-8; **36**, 79823-87-3; **37**, 124919-49-9; **38**, 124919-50-2; **39**, 124919-51-3; **40**, 124919-52-4.