134. Synthesis and Biological Evaluation of 14-Alkoxymorphinans

Part 4[1])

Opioid Agonists and Partial Opioid Agonists in a Series of *N*-(Cyclobutylmethyl)-14-methoxymorphinan-6-ones

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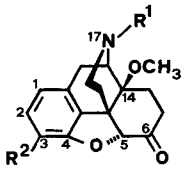
The *N*-(cyclobutylmethyl)morphinans **12**, **19**, **20**, **21**, **27**, and **29** and the *N*-(2-cyanoethyl) analogue **33** were prepared from different precursors. Pharmacological evaluation (*e.g.* opioid receptor binding assays, acetic-acid writhing test, hot-plate assay) points to a partial opioid agonism of compounds **12**, **27**, **29**, and **33**, and to full opioid agonism of compounds **19**–**21**.

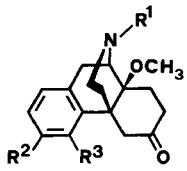
Introduction. – A series of 14-methoxy-*N*-methylmorphinan-6-ones was found to possess marked opioid agonist activities [2]. The most potent derivatives were compounds **1**, **2**, **3**, and **4**. Replacement of the *N*-Me group of **1** by allyl and cyclopropylmethyl groups gave 14-*O*-methylnaloxone (**5**) and 14-*O*-methylnaltrexone (**6**), respectively, which exhibited similar opioid antagonist properties in comparison to the 14-OH analogues naloxone and naltrexone [3]. When the *N*-Me group of **2**, **3**, and **4** was replaced by allyl and/or cyclopropylmethyl groups to give compounds **7**–**11**, opioid antagonism and selectivity for μ opioid receptors was obtained [1] [4–6]. Cyprodime (**8**), the most promising compound of this series, has been tritium-labeled and is being used as pharmacological tool [7].

In view of these findings, it was of interest to replace the *N*-Me group of compounds **1**–**4** by a cyclobutylmethyl group to obtain potential partial agonists. We speculated that these derivatives would show the opioid-type side effects to a lesser extent than the *N*-Me analogues [2].

Chemistry. – Compound **12** was prepared starting from the 3-*O*-benzylated morphinan **13** which is readily available from oxymorphone [2]. *N*-Demethylation was accomplished with 2,2,2-trichloroethyl chloroformate. The resulting carbamate **14** was cleaved reductively with Zn/NH_4Cl in 80% AcOH to give *N*-normorphinan **15** which was first acylated in DMF with cyclobutanecarbonyl chloride to afford amide **16**. Reduction of **16** with LAH yielded a mixture of epimeric alcohols **17** which was oxidized by *Oppenauer*

[1]) Part 3: [1].





1 $R^1 = CH_3$, $R^2 = OH$
5 $R^1 = CH_2CH{=}CH_2$, $R^2 = OH$
6 R^1 = CPM, $R^2 = OH$
12 R^1 = CBM, $R^2 = OH$
13 $R^1 = CH_3$, $R^2 = OCH_2Ph$
14 $R^1 = CO_2CH_2CCl_3$, $R^2 = OCH_2Ph$
15 $R^1 = H$, $R^2 = OCH_2Ph$
16 R^1 = CBC, $R^2 = OCH_2Ph$
17 R^1 = CBM, $R^2 = OCH_2Ph$
(mixture of C(6)-epimeric alcohols)
18 R^1 = CBM, $R^2 = OCH_2Ph$
22 $R^1 = CH_3$, $R^2 = H$
23 $R^1 = CO_2CH_2CCl_3$, $R^2 = H$
24 $R^1 = R^2 = H$
25 R^1 = CBC, $R^2 = H$
26 R^1 = CBM, $R^2 = H$
(mixture of C(6)-epimeric alcohols)
27 R^1 = CBM, $R^2 = H$

2 $R^1 = CH_3$, $R^2 = H$, $R^3 = OCH_3$
3 $R^1 = CH_3$, $R^2 = R^3 = OCH_3$
4 $R^1 = CH_3$, $R^2 = R^3 = H$
7 $R^1 = CH_2CH{=}CH_2$, $R^2 = H$, $R^3 = OCH_3$
8 R^1 = CPM, $R^2 = H$, $R^3 = OCH_3$ (cyprodime)
9 $R^1 = CH_2CH{=}CH_2$, $R^2 = R^3 = OCH_3$
10 R^1 = CPM, $R^2 = R^3 = OCH_3$
11 R^1 = CPM, $R^2 = R^3 = H$
19 R^1 = CBM, $R^2 = H$, $R^3 = OH$
20 R^1 = CBM, $R^2 = H$, $R^3 = OCH_3$
21 R^1 = CBM, $R^2 = R^3 = H$
28 R^1 = CBM, $R^2 = H$, R^3 = PTO
29 R^1 = CBM, $R^2 = R^3 = OCH_3$
30 $R^1 = H$, $R^2 = R^3 = OCH_3$
31 R^1 = CBC, $R^2 = R^3 = OCH_3$
32 R^1 = CBM, $R^2 = R^3 = OCH_3$
(mixture of C(6)-epimeric alcohols)
33 $R^1 = CH_2CH_2CN$, $R^2 = R^3 = OCH_3$

CBC = cyclobutylcarbonyl
CBM = cyclobutylmethyl
CPM = cyclopropylmethyl
PTO = 1-phenyl-1*H*-tetrazol-5-yloxy

oxidation to give compound **18**. Catalytic hydrogenation over Pd/C afforded the desired hydroxy derivative **12**.

Compounds **19**, **20**, and **21** were synthesized starting from **22** which is available from oxymorphone in six steps [2]. *N*-Demethylation was performed *via* the carbamate **23** which was cleaved reductively as described above for **14** [1]. Acylation with cyclobutanecarbonyl chloride followed by LAH reduction of the amide **25** gave a mixture of epimeric alcohols **26**. *Oppenauer* oxidation yielded compound **27** in which the 4,5-epoxy bridge was cleaved reductively with Zn/NH_4Cl in refluxing MeOH to give the hydroxy compound **19**. Treatment of **19** with $Me_3(Ph)NCl$ afforded the 4,14-dimethoxymorphinan **20**. To obtain the aromatic unsubstituted analogue **21**, **19** was first alkylated with 5-chloro-1-phenyl-1*H*-tetrazole in DMF, followed by catalytic hydrogenation over Pd/C of the resulting tetrazolyl ether **28** to give **21**.

The 3,4,14-trimethoxy derivative **29** was prepared from *N*-normorphinan **30** [1] by acylation with cyclobutanecarbonyl chloride, followed by LAH reduction of the amide **31**, and *Oppenauer* oxidation of the epimeric alcohols **32**.

A differently *N*-substituted analogue **33** has also been prepared to obtain a potential partial agonists. The 2-cyanoethyl group known to produce opioid agonists in morphinans with less side effects [8] was introduced by alkylation of **30** with acrylonitrile to yield **33**.

Pharmacological Evaluation. – In vitro *Studies*. Opioid receptor binding assays (ORBA) were performed to determine μ opioid receptor affinity and κ receptor affinity. The affinity for μ receptors was evaluated using [^{3}H]naloxone (antagonist with preference for μ receptors) as ligand. The affinity for κ receptors was determined with [^{3}H]tifluadom (κ-selective agonist) as ligand *(Table 1)*.

Table 1. *Opioid Receptor Binding Assays (ORBA)*[a])

Compound	[^{3}H]Naloxone			[^{3}H]Tifluadom
	+NaCl	−NaCl	Ratio ± NaCl	
12	2.25	0.70	3.2	3.6
19	85	6.5	13	153
20	55	9.5	5.8	248
21	230	29	7.9	302
27	900	180	5.0	1670
29	180	180	1.0	180
33	275	100	2.7	1700
Cyprodime	4.5	90	0.05	170
Morphine	65.5	2.0	33	162
Levallorphan	1.1	0.54	2.0	0.67

[a]) The values are IC_{50} in nM. The unlabeled drugs were examined with at least 5 concentrations in duplicate in two independent determinations in the presence of [^{3}H]ligands.

For evaluating opioid agonist/antagonist properties of the compounds, the sodium shift (presence and absence of Na^+) of [^{3}H]naloxone binding was used [9], although it should be kept in mind that in the presence of Na^+, [^{3}H]naloxone labels also κ receptors [10]. Morphine-like drugs have low affinity for κ receptors, and, therefore, their binding is decreased in the presence of Na^+. Thus, the exact meaning of the sodium shift is not clear, since in the presence of Na^+, [^{3}H]naloxone still labels μ receptors.

Compounds **12**, **27**, **29**, and **33** were partial agonists. Compound **12**, the most potent partial agonist had similar receptor affinities as levallorphan. Compounds **27** and **33** showed preference for rather μ than κ receptors.

Compounds **19–21** were full agonists and exhibited preference for μ receptors.

In vivo *Studies*. Opioid agonism was determined using the AcOH-writhing test (AW) and the hot-plate assay (HP) in mice *(Table 2)*. The compounds produced a pattern of opioid antinociception, ranging from full agonists, very active in the AW and HP (**19** and **21**) to presumable partial agonists (**12**, **20**, **27**, **29**, and **33**) being rather active in the AW but having weak or no effect in the HP.

Table 2. *AcOH-Writhing Test* (AW) *and Hot-plate Assay* (HP) *in Mice*

Compound	AcOH-writhing test ED_{50} [mg/kg, s.c.][a])	Hot-plate test ED_{50} [mg/kg, s.c.][a])
12	0.037 (0.008–0.17)	~ 30
19	1.6 (0.82–3.1)	3.4 (2.1–5.4)
20	1.3 (0.90–1.8)	> 30
21	0.55 (0.31–1.0)	3.8 (1.6–9.2)
27	5.0 (3.2–7.8)	> 30
29	0.45 (0.23–0.88)	> 30
33	1.6 (0.66–3.8)	> 30
Cyprodime	> 10	> 30
Morphine	0.52 (0.27–0.99)	2.9 (1.7–5.0)
Levallorphan	1.5 (0.24–9.3)	> 30

[a]) The ED_{50} values represent the effective dose at which 50% of the animals showed an analgesic response.

Table 3. *Opioid-Type Withdrawal Jumping Inhibition* (IWJ) *and Precipitation* (PWJ) *Test in Mice and Respiratory Activity Test* (RA) *in Rabbits*

Compound	IWJ	PWJ	RA	
	ED_{50} [mg/kg, s.c.][a])	ED_{50} [mg/kg, s.c.][a])	Dose [mg/kg, i.v.]	%-Change of volume (±SE)
12	1.3	0.88	0.01[b])	−29 (±4.3)
27	–	–	3.0	−39 (±3.2)
29	1.1	26	1.0	−32 (±3.4)
33	–	–	1.0	−21 (±5.6)
Cyprodime	–	0.6	1.0	+21 (±5.2)
Morphine	21	–	1.0	−38 (±3.3)
Levallorphan	–	0.29	1.0	−3.8 (±3.3)

[a]) The ED_{50} values represent the effective dose at which 50% of the animals were effected.
[b]) Bell-shaped dose-response curve, dose and effect in apex.

Opioid agonism and antagonism was tested in the opioid-type withdrawal jumping inhibition (IWJ) and precipitation (PWJ) test in mice *(Table 3)*. The compounds tested (**12** and **29**) displayed partial agonist properties in the IWJ and PWJ.

Opioid agonism and antagonism was also tested in the respiratory activity test in rabbits (RA; *Table 3*). All the compounds tested (**12**, **27**, **29**, and **33**) induced depression of respiration.

Discussion and Conclusion. – Compounds **19**–**21** with ratios ±NaCl of *ca.* 10 in the ORBA point to full opioid agonism which was confirmed for **19** and **21** in the AW and HP, while **20**, which exhibited the lowest ratio of these three compounds, seems to be a partial agonist in the AW and HP. All three compounds exhibited preference for μ rather than κ opioid receptors in the ORBA.

Compounds **12**, **27**, **29**, and **33** were found to have a ratio ±NaCl in the ORBA pointing to partial agonism in the ORBA. These findings were confirmed in the AW and HP, with **12** showing the highest antinociceptive potency in the AW (*ca.* 15 times more potent than morphine). Partial agonism of **12** and **29** in the ORBA was verified in the IWJ and PWJ. In the RA, all the tested derivatives (**12**, **27**, **29**, and **33**) exhibited a decrease in respiratory volume to a similar extent as morphine, indicating μ agonism.

Thus, replacement of the *N*-Me group by a *N*-cyclobutylmethyl group in the 14-methoxymorphinan-6-one series resulted in compounds with pure opioid agonism (**19** and **21**) and partial agonism (**12**, **20**, **27**, and **29**). All these compounds showed intrinsic activity at μ rather than at κ opioid receptors which leads to opioid-type side effects (*e.g.* inhibition of withdrawal jumping behaviour and respiration depression).

Introduction of a *N*-(2-cyanoethyl) group (compound **33**) gave a partial agonist which also exhibited intrinsic activity at μ rather than at κ receptors.

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Experimental Part

Chemistry. – *General.* CC: basic alumina (70–230 mesh ASTM) from *Merck*. M.p.: *Kofler* melting-point microscope; uncorrected. $[\alpha]_D$: *c* in g/100 ml, *Perkin Elmer 141* polarimeter. IR spectra (in cm^{-1}): *Beckman Accu Lab 2* apparatus. ^{1}H-NMR spectra: *Jeol-JNM-PMX-60* spectrometer; δ in ppm relative to TMS as internal reference, *J* (apparent coupling constant) in Hz. EI-MS and CI-MS: *Finnigan MAT 44S* apparatus.

(−)-3-Benzyloxy-4,5α-epoxy-14-methoxymorphinan-6-one Hydrobromide (**15**·HBr). 2,2,2-Trichloroethyl chloroformate (24.35 ml, 172.7 mmol) was added dropwise to a refluxing mixture of **13** [2] (8.4 g, 17.3 mmol), $KHCO_3$ (8.65 g, 86.5 mmol), and 120 ml of EtOH-free $CHCl_3$ within 15 min while stirring. After 4 h, more 2,2,2-trichloroethyl chloroformate (12 ml, 85.1 mmol) and $KHCO_3$ (8.65 g, 86.5 mmol) were added and the resulting mixture was stirred under reflux for another 24 h. Then the inorg. solid was filtered off and the filtrate was evaporated at 95° (bath temp.) at first at 10 Torr, then at 0.1 Torr. The resulting residue (13.4 g colorless glassy solid) was used for the next step without further purification and characterization. This glassy solid was dissolved in 60 ml glacial AcOH, then 15 ml of H_2O were added. The soln. was cooled to 10°, activated Zn powder (6 g, 91.8 mmol) was added in small portions while stirring vigorously within 5 min (the temp. raised to 25°). The mixture was cooled to 10°, and another 6 g of Zn powder were added within 5 min (the temp. remained at 10°). After stirring at r.t. for 3.5 h, the mixture was filtered, the filtrate diluted with *ca.* 120 ml of H_2O, washed with Et_2O (2 × 100 ml), alkalized with conc. NH_4OH, and extracted with $CHCl_3$ (2 × 80 ml). The combined org. layers were dried and evaporated to give 6.1 g of a colorless oil which was converted into the HBr salt (**15**·HBr; 4.8 g, 57%; crystallized from acetone) in the usual way. A small portion of this material was recrystallized from EtOH for analysis. M.p. 217–219°. $[\alpha]_D^{20} = -116.9$ (*c* = 0.83, MeOH). IR (KBr): 3400 ($^+NH_2$), 1715 (CO). ^{1}H-NMR ((D$_6$)DMSO): 9.05, 8.30 (2*s*, $^+NH_2$); 7.30 (*m*, 5 arom. H); 6.86 (*d*, *J* = 8, 1 arom. H); 6.65 (*d*, *J* = 8, 1 arom. H); 5.09 (*s*, CH_2O); 4.96 (*s*, H–C(5)); 3.32 (*s*, CH_3O). EI-MS: 391 (M^+). Anal. calc. for $C_{24}H_{25}NO_4 \cdot HBr$ (472.38): C 61.02, H 5.55, N 2.97, Br 16.92; found: C 61.00, H 5.72, N 2.88, Br 16.86.

(−)-17-(Cyclobutylmethyl)-4,5α-epoxy-3-hydroxy-14-methoxymorphinan-6-one (**12**). A mixture of **15**·HBr (3 g, 6.35 mmol), cyclobutylcarbonyl chloride (1.13 g, 9.53 mmol), K_2CO_3 (5 g, 39 mmol), and 20 ml of anh. DMF was stirred at 35° (bath temp.) under N_2 for 4 h. The inorg. material was filtered off, the filtrate evaporated, the oily residue partitioned between AcOEt and 1N HCl, the AcOEt phase washed with H_2O, dried, and evaporated to yield 2.5 g of **16** as a slightly yellow foam (EI-MS: 473 (M^+)) which was not further purified. A soln. of this foam (2.1 g) in 2 ml of anh. CH_2Cl_2 and 40 ml of anh. Et_2O was added dropwise to an ice-cooled and stirred suspension of LAH (800 mg, 21.1 mmol) in 50 ml of anh. Et_2O under N_2 within 15 min. The resulting mixture was refluxed for 1 h, then 100 ml of sat. Na_2SO_4 soln. were added dropwise, and the org. phase was separated. The aq. layer was extracted with AcOEt (2 × 30 ml), the combined org. layers were dried and evaporated to give 1.95 g of **17** (TLC: mixture of epimeric alcohols) as a slightly brown oil which was not further purified and characterized. A soln. of this oil (1.95 g), benzophenone (16 g, 87.8 mmol), and 120 ml of anh. toluene was concentrated *in vacuo* to *ca.* half of the original volume and then added dropwise to a slurry of $(CH_3)_3COK$ (3 g, 26.7 mmol) and 80 ml of anh. toluene within 10 min at r.t. under N_2 while stirring. This mixture was stirred for 5 h at 90° (bath temp.). After cooling, ice and 2N HCl (150 ml) were added, the layers separated, the aq. layer was washed with Et_2O (3 × 100 ml), alkalized with conc. NH_4OH soln., and extracted with CH_2Cl_2 (2 × 40 ml). The combined org. layers were dried and evaporated to give 1.68 g of a brown oil which was chromatographed on alumina basic grade II (length of the column 12 cm, diameter 3.5 cm, elution with CH_2Cl_2) to yield TLC-pure **18** as colorless oil (750 mg) which was not further characterized. A mixture of this oil, 200 mg of 10% Pd/C catalyst, and 60 ml of 95% EtOH was hydrogenated at r.t. and 40 psi for 4 h. The catalyst was filtered off and the filtrate evaporated to give 570 mg of a colorless crystalline solid which was recrystallized from MeOH to yield 495 mg of **12**. M.p. 88–90°. $[\alpha]_D^{20} = -181.4$ (*c* = 1.31, $CHCl_3$). IR (KBr): 3500, 3400 (OH), 1715 (CO). ^{1}H-NMR ($CDCl_3$): 6.67 (*d*, *J* = 8, 1 arom. H); 6.48 (*d*, *J* = 8, 1 arom. H); 4.57 (*s*, H–C(5)); 3.46 (*s*, CH_3O); 3.27 (*s*, CH_3O). EI-MS: 369 (M^+). Anal. calc. for $C_{22}H_{27}NO_4 \cdot MeOH$ (401.50): C 68.80, H 7.78, N 3.49; found: C 69.02, H 7.78, N 3.52.

(−)-17-(Cyclobutylcarbonyl)-4,5α-epoxy-14-methoxymorphinan-6-one (**25**). A mixture of **24** [1] (6.1 g base, 21.4 mmol), K_2CO_3 (5 g, 36.2 mmol), cyclobutylcarbonyl chloride (3.3 g, 27.8 mmol), and CH_2Cl_2 (40 ml) was stirred under reflux for 26 h. The inorg. solid was filtered off, the filtrate washed with 100 ml of H_2O and brine, dried, and evaporated to give 7.5 g of a colorless crystalline solid, which was treated with boiling MeOH to afford 7.15 g (91%) of pure **25**. M.p. 208–210°. IR (KBr): 1710 (CO), 1620 (amide). EI-MS: 367 (M^+). Anal. calc. for $C_{22}H_{25}NO_4$ (367.43): C 71.91, H 6.86, N 3.81; found: C 71.97, H 6.71, N 3.89.

(−)-17-(Cyclobutylmethyl)-4,5α-epoxy-14-methoxymorphinan-6-one Hydrobromide (**27**·HBr). A soln. of **25** (5 g, 13.6 mmol) in 5 ml of anh. CH_2Cl_2 and 20 ml of anh. Et_2O was added dropwise to an ice-cooled and stirred

suspension of LAH (1.5 g, 39.5 mmol) and 50 ml of anh. Et_2O under N_2 within 10 min. This mixture was stirred under reflux for 1 h, then 150 ml of sat. Na_2SO_4 soln. were added dropwise to the refluxing mixture. The org. layer was separated and the aq. layer extracted with AcOEt (2 × 50 ml). The combined org. layers were dried and evaporated to give 4.8 g of **26** as a colorless crystalline solid. This mixture of epimeric alcohols (TLC) was not further characterized. It was dissolved in 300 ml of toluene together with benzophenone (48 g, 0.26 mol), and this soln. was concentrated *in vacuo* to *ca.* 250 ml. This soln. was added dropwise to a slurry of $(CH_3)_3COK$ (9 g, 80.2 mmol) and 150 ml of anh. toluene at r.t. under N_2 within 20 min. The resulting mixture was stirred at 90° (bath temp.) for 7 h, then cooled, 200 ml of ice-water and 200 ml of 2N HCl added. The aq. layer was separated and the org. layer was extracted with 2N HCl (2 × 50 ml). The combined aq. layers were washed with Et_2O (6 × 100 ml), alkalized with conc. NH_4OH soln., and extracted with Et_2O (3 × 80 ml). The Et_2O phase was dried and evaporated to give 4.65 g of a violet foam which was chromatographed on basic alumina grade II (length of the column 15 cm, diameter 3.5 cm, elution with CH_2Cl_2) to yield 4.05 g (84%) of TLC-pure **27** as a colorless solid. A portion of this material was converted into the HBr salt in the usual way: m.p. 281–283° (dec.; MeOH/Et_2O). $[\alpha]_D^{20} = -184.6$ ($c = 0.73$, MeOH). IR (KBr): 3400 ($^+$NH), 1715 (CO). ^{1}H-NMR ((D$_6$)DMSO): 8.64 (br. *s*, $^+$NH); 7.27–6.63 (*m*, 3 arom. H); 4.95 (*s*, H–C(5)); 3.34 (*s*, CH_3O). Anal. calc. for $C_{22}H_{27}NO_3 \cdot HBr$ (434.37): C 60.83, H 6.50, N 3.22, Br 18.40; found: C 60.64, H 6.66, N 3.22, Br 18.34.

(–)-17-(Cyclobutylmethyl)-4-hydroxy-14-methoxymorphinan-6-one Hydrobromide (**19**·HBr). Activated Zn powder (4.6 g, 69 mmol) was added in portions to a refluxing mixture of **27** (2.3 g base, 6.51 mmol), NH_4Cl (4.6 g, 85 mmol), and MeOH (100 ml) within 5 min. The mixture was stirred under reflux for additional 30 min, filtered, and washed with MeOH, and the filtrate evaporated. The oily residue was alkalized with conc. NH_4OH soln. and extracted with $CHCl_3$/i-PrOH 3:1. The org. layer was washed with H_2O and brine, dried, and evaporated to yield 2.2 g of a slightly brown foam which was converted into the HBr salt (**19**·HBr; 2.15 g, 76%) in the usual way. M.p. 296–300° (dec.; MeOH/Et_2O). $[\alpha]_D^{20} = -77.3$ ($c = 0.94$, MeOH). IR (KBr): 3440, 3170 (OH, $^+$NH), 1710 (CO). ^{1}H-NMR ((D$_6$)DMSO): 9.64, 8.58 (2*s*, OH, $^+$NH); 7.15–6.56 (*m*, 3 arom. H); 3.33 (*s*, CH_3O). Anal. calc. for $C_{22}H_{29}NO_3 \cdot HBr$ (436.39): C 60.55, H 6.93, N 3.21, Br 18.31; found: C 60.25, H 7.19, N 3.19, Br 18.40.

(–)-17-(Cyclobutylmethyl)-4,14-dimethoxymorphinan-6-one (**20**). A mixture of K_2CO_3 (1 g, 7.8 mmol) and 30 ml of anh. DMF was gassed at r.t. with N_2 for 30 min. Then, **19**·HBr (600 mg, 1.37 mmol) and $Me_3(Ph)NCl$ (708 mg, 4.12 mmol) were added and the resulting mixture was stirred under N_2 and at 80° (bath temp.) for 5 h. After filtration, the filtrate was evaporated to give a slightly brown crystalline solid which was dissolved in dil. AcOH. The pH was adjusted to 6–6.5 with conc. NH_4OH soln., washed with cyclohexane (2 × 20 ml), alkalized with conc. NH_4OH soln., and extracted with CH_2Cl_2 (3 × 10 ml). The combined org. layers were dried and evaporated to yield 350 mg of a slightly brown oil which was crystallized from EtOH to afford 320 mg (63%) of **20**. For analysis, a portion was recrystallized from EtOH. M.p. 118–120°. $[\alpha]_D^{20} = -77.1$ ($c = 1.47$, MeOH). ^{1}H-NMR ($CDCl_3$): 7.15–6.52 (*m*, 3 arom. H); 3.78 (*s*, CH_3O–C(4)); 3.30 (*s*, CH_3O–C(14)). Anal. calc. for $C_{23}H_{31}NO_3$ (369.51): C 74.76, H 8.46, N 3.79; found: C 74.43, H 8.64, N 3.67.

(–)-17-(Cyclobutylmethyl)-14-methoxymorphinan-6-one Salicylate (**21**·Salicylic Acid). A mixture of **19**·HBr (1 g, 2.29 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (600 mg, 3.33 mmol), K_2CO_3 (2.5 g, 18.1 mmol), and 20 ml of anh. DMF was stirred at r.t. under N_2 for 60 h. After addition of 120 ml of H_2O and extraction with Et_2O (3 × 30 ml), the org. layer was washed with H_2O (3 × 30 ml) and brine (15 ml), dried, and evaporated to give 950 mg of a slightly brown oil which was crystallized from MeOH to yield 736 mg of **28**. M.p. 196–199°. ^{1}H-NMR ($CDCl_3$): 8.20–6.93 (*m*, 8 arom. H); 3.28 (*s*, CH_3O). CI-MS: 500 ($M^+ + 1$). Compound **28** (500 mg, 1.0 mmol) was dissolved in 60 ml of glacial AcOH, then 10% Pd/C catalyst (500 mg) was added. This mixture was hydrogenated at 35° and 45 psi for 26 h. The catalyst was filtered off, the filtrate evaporated, the oily residue alkalized with conc. NH_4OH soln. and extracted with CH_2Cl_2 (3 × 5 ml). The combined org. layers were washed with brine, dried, and evaporated to give 350 mg of a slightly brown oil which was converted into the salicylate (**21**·salicylic acid; 360 mg) in the usual manner. A portion was recrystallized from MeOH/Et_2O. M.p. 181–183°. $[\alpha]_D^{20} = -69.4$ ($c = 1.11$, $CHCl_3$). IR (KBr): 3400 ($^+$NH), 1700 (CO). ^{1}H-NMR ($CDCl_3$): 11.94 (br. *s*, OH, $^+$NH); 7.92–6.75 (*m*, 8 arom. H); 3.39 (*s*, CH_3O). Anal. calc. for $C_{22}H_{29}NO_2 \cdot C_7H_6O_3$ (477.60): C 72.93, H 7.39, N 2.93; found: C 72.57, H 7.51, N 2.80.

(–)-17-(Cyclobutylcarbonyl)-3,4,14-trimethoxymorphinan-6-one (**31**). A mixture of **30**·oxalic acid [1] (2.55 g, 6.05 mmol), cyclobutylcarbonyl chloride (1.15 g, 9.7 mmol), K_2CO_3 (4 g, 28.9 mmol), and 10 ml of anh. DMF was stirred under N_2 at 40° (bath temp.) for 1 h. The mixture was poured on 200 ml of ice-water, extracted with AcOEt (3 × 20 ml), the combined org. layers were washed with 1N HCl, H_2O, and brine, dried, and evaporated to give 2.2 g of a colorless crystalline solid which was treated with MeOH to yield 1.95 g (78%) of **31**. An anal. sample was

obtained by recrystallization of a small sample from MeOH. M.p. 177–178°. IR (KBr): 1710 (CO), 1630 (amide). ^{1}H-NMR ($CDCl_3$): 6.70 (*s*, 2 arom. H); 3.91 (*s*, CH_3O); 3.75 (*s*, CH_3O); 3.26 (*s*, CH_3O–C(14)). CI-MS: 414 ($M^+ + 1$). Anal. calc. for $C_{24}H_{31}NO_5$ (413.51): C 69.71, H 7.56, N 3.39; found: C 69.52, H 7.83, N 3.32.

(−)-17-(Cyclobutylmethyl)-3,4,14-trimethoxymorphinan-6-one (**29**). A soln. of **31** (1.6 g, 3.87 mmol) in 2 ml of anh. CH_2Cl_2 and 50 ml of anh. Et_2O was added dropwise to an ice-cooled and stirred suspension of LAH (0.5 g, 13.2 mmol) in 30 ml of anh. Et_2O within 15 min under N_2. The resulting mixture was stirred under reflux for 1 h, then 100 ml of sat. Na_2SO_4 soln. were added dropwise to the refluxing mixture. The org. layer was separated, the aq. layer washed with Et_2O (2 × 30 ml), and the combined org. layers were dried and evaporated. The residue, 1.5 g colorless foam of **32** (mixture of epimeric alcohols by TLC), was used for the next step without further purification and characterization. The residue was dissolved together with benzophenone (8 g, 43.9 mmol) in 40 ml of anh. toluene, and this soln. was concentrated *in vacuo* to *ca.* 30 ml. This soln. was added dropwise to a slurry of $(CH_3)_3COK$ (1.5 g, 13.4 mmol) and 40 ml of anh. toluene at r.t. under N_2 within 10 min. This mixture was stirred at 90° (bath temp.) for 5 h, cooled, and 100 ml of ice-water and 100 ml of 2N HCl were added. The aq. layer was separated, the org. layer extracted with 2N HCl (2 × 10 ml), the combined aq. layers were washed with Et_2O (3 × 80 ml), alkalized with conc. NH_4OH soln., extracted with Et_2O (3 × 30 ml), dried, and evaporated to give 1.23 g of a slightly brown crystalline solid which was recrystallized from MeOH to yield 710 mg of **29** (m.p. 136–138°). The mother liquor was evaporated and chromatographed on alumina basic grade III (length of the column 25 cm, diameter 1.1 cm, elution with CH_2Cl_2) to give 415 mg of a colorless crystalline solid which was recrystallized from MeOH to yield another 220 mg of **29** (m.p. 138–139°, anal. sample). Total yield 930 mg (60%). $[\alpha]_D^{20} = -94.1$ ($c = 0.94$, $CHCl_3$). IR (KBr): 1705 (CO). ^{1}H-NMR ($CDCl_3$): 6.65 (*s*, 2 arom. H); 3.87 (*s*, CH_3O); 3.73 (*s*, CH_3O); 3.29 (*s*, CH_3O–C(14)). CI-MS: 400 ($M^+ + 1$). Anal. calc. for $C_{24}H_{33}NO_4$ (399.53): C 72.15, H 8.33, N 3.51; found: C 71.80, H 8.64, N 3.47.

(−)-17-(2-Cyanoethyl)-3,4,14-trimethoxymorphinan-6-one (**33**). A soln. of **30** [1] (440 mg of base, 1.33 mmol), acrylonitrile (0.1 ml, 1.53 mmol), Et_3N (0.74 ml, 5.31 mmol), and 20 ml of 95% EtOH was refluxed for 6.5 h. After evaporation, the oily residue was chromatographed on alumina basic grade II (length of the column 25 cm, diameter 1.1 cm, elution with CH_2Cl_2) to yield 355 mg of a colorless foam which was crystallized from MeOH to give 335 mg (66%) of **33**. M.p. 185–187°. $[\alpha]_D^{20} = -83.5$ ($c = 0.79$, $CHCl_3$). IR (KBr): 2240 (CN), 1700 (CO). ^{1}H-NMR ($CDCl_3$): 6.67 (*s*, 2 arom. H); 3.90 (*s*, CH_3O); 3.79 (*s*, CH_3O); 3.34 (*s*, CH_3O–C(14)). EI-MS: 384 (M^+). Anal. calc. for $C_{22}H_{28}N_2O_4$ (384.48): C 68.73, H 7.34, N 7.29; found: C 68.59, H 7.30, N 7.28.

Pharmacology. – *Drugs Used.* Compounds **12**, **20**, and **29** were used as bases, **19**, **27**, and cyprodime as HBr salts, and **21** as salicylate. Other compounds and their sources included: levallorphan tartrate, and [^{3}H]tifluadom *(Roche)*, morphine hydrochloride *(Sandoz)*, naloxone hydrochloride *(Endo)*, and [^{3}H]naloxone *(New England Nuclear)*. For *in vitro* experiments, the compounds were dissolved in the vehicles indicated in the respective methods. In *in vivo* experiments, they were dissolved in saline for parenteral injection and tap water for peroral administration; sometimes, 1N HCl had to be added in order to obtain a soln. The volume of injection was 10 ml/kg in mice and 1.5 ml/kg in rabbits.

Opioid Receptor Binding Assays. [^{3}H]Naloxone binding was performed essentially as described by *Pert* and *Snyder* [9]. [^{3}H]Tifluadom binding was performed in homogenates of guinea-pig cerebellum as described by *Burkard et al.* [11] and *Gillan et al.* [12]. IC_{50} values were determined graphically or by computer-program-assisted least-squares fit of sigmoid curves. All experiments, performed in duplicate, were replicated at least once with similar results.

AcOH-Writhing Test. This test was performed as described by *Witkin et al.* [13].

Hot-Plate Test. This test was performed as described by *Woolfe et al.* [14].

Opioid-Type Withdrawal Inhibition and Precipitation Test. These tests were performed as described in [2].

Respiratory Activity Test. This test was performed as described in [2].

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