Synthesis and Biological Evaluation of 14-Alkoxymorphinans. 1. Highly Potent Opioid Agonists in the Series of (–)-14-Methoxy-*N*-methylmorphinan-6-ones†

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A series of eight (–)-14-methoxymorphinan-6-ones was synthesized and biologically evaluated. The morphinanones **3–7** were prepared from 3-desoxy-7,8-dihydro-14-hydroxymorphinone (**1**). The key step in this synthetic sequence, O-methylation in position 14, was accomplished with dimethyl sulfate. Hydrolysis followed by reductive opening of the 4,5-oxygen bridge afforded the phenol **4**, which was O-methylated to give **5**. Removal of the 4-OH group yielded the aromatic unsubstituted morphinan **7**. The synthesis of **9** and **10** was accomplished by starting from 14-methoxy-7,8-dihydrocodeinone and involved a similar reaction sequence. The compounds **12–15** were synthesized from oxymorphone (**11**), which was 3-O-benzylated, 6,14-bis-O-methylated with dimethyl sulfate, hydrolyzed, and hydrogenated to yield the oxymorphone 14-*O*-methyl ether **15**. The derivatives **3, 4, 5, 7, 9, 10, 14,** and **15** exhibited high antinociceptive potency in the hot-plate assay in mice, after both subcutaneous and oral administration. The most potent derivative in this series (**15**) showed a potency (sc) about 400 times higher than that of morphine and about 40 times higher than its 14-OH analogue oxymorphone (**11**). The 14-OCH_3 series also exhibited a considerably higher affinity to opioid receptors in binding studies using [^{3}H]naloxone as ligand when compared to their 14-OH analogues.

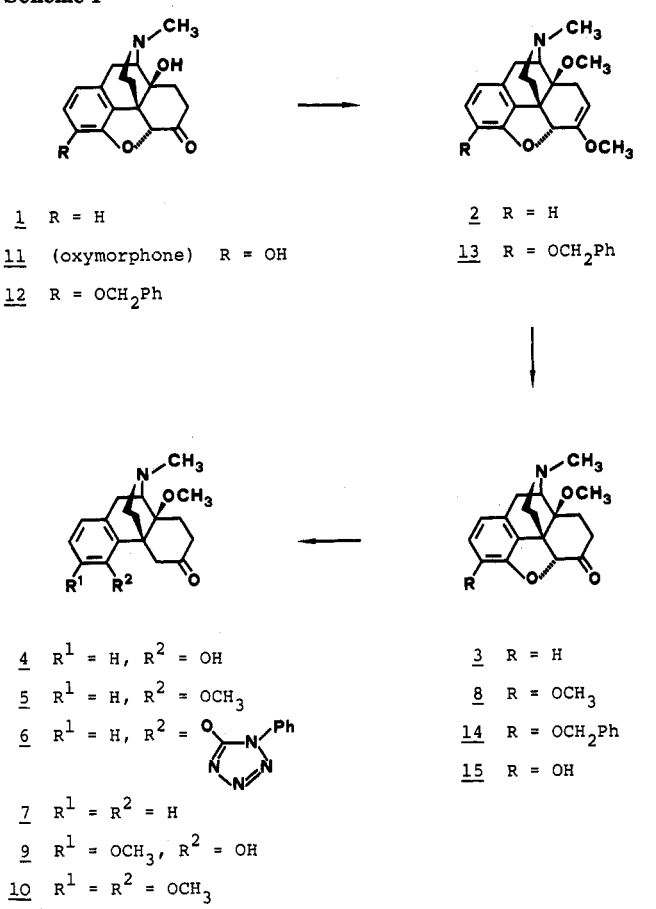
N-Methylmorphinan-6-ones of the natural series of opioids exhibit high antinociceptive potency when oxygenated at C-4, dioxygenated at C-3,4, or when the aromatic ring is unsubstituted.[1] Hydroxylation at C-14 does not significantly alter the opioid agonist activity. C-14 *O*-alkyl ethers of the opioid antagonists naloxone and naltrexone have been recently prepared and pharmacologically evaluated.[2] No major changes in the quality of action of naloxone or naltrexone were found after C-14 *O*-alkylation. The C-14 *O*-alkyl analogues, however, exhibited a slightly higher affinity to the opioid receptors.

Therefore, in order to further elaborate on the effect of C-14 *O*-alkyl substitution in opioid agonist morphinan-6-ones, we decided to prepare some novel 14-methoxy-*N*-methylmorphinan-6-ones and to compare this series pharmacologically with the analogues of the C-14 OH series, which had been prepared previously.[3-5]

Chemistry. The synthetic sequence used to prepare the 14-methoxy-*N*-methylmorphinan-6-ones is shown in Scheme I. The 4,5-epoxymorphinanone **1**, prepared from oxymorphone (**11**),[4] served as a starting material to synthesize compounds **2–7**. Alkylation of **1** with 2.2 equiv of dimethyl sulfate at 0 °C in the presence of an excess of sodium hydride in DMF yielded the enol ether **2**, which was hydrolyzed to give the ketone **3**. Reductive cleavage of the 4,5-oxygen bridge was achieved with activated Zn/NH_4Cl in refluxing methanol to yield the phenol **4**, which was O-methylated with phenyltrimethylammonium chloride in DMF in the presence of potassium carbonate to give the *O*-methyl ether **5**. In order to remove the 4-OH group in **4**, this compound was treated with 5-chloro-1-phenyl-1*H*-tetrazole in DMF in the presence of potassium carbonate to give the phenyltetrazolyl ether **6**, which was hydrogenated in glacial acetic acid over 10% Pd/C at room temperature to afford the aromatic unsubstituted morphinanone **7**.

The C-3,4 dioxygenated compounds **9** and **10** were prepared from 14-methoxydihydrocodeinone (**8**), which was synthesized according to a published procedure from 14-hydroxycodeinone in two steps.[2,6,7] Compound **8** was

Scheme I



† This paper is dedicated to Prof. Dr. H. Bretschneider on the occasion of his 80th birthday.

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converted into 14-methoxydihydrothebainone (9) by treatment with activated Zn/NH_4Cl in refluxing methanol.[6] O-Methylation of 9 with phenyltrimethylammonium chloride in DMF in the presence of potassium carbonate afforded the trimethoxymorphinanone 10.

The synthesis of the oxymorphone analogue 15 was accomplished by using oxymorphone (11) as a starting material. Oxymorphone was benzylated to give the known benzyl ether 12,[8] which was treated with sodium hydride and further alkylated with 2.2 equiv of dimethyl sulfate in DMF at room temperature to afford the enol ether 13. Hydrolysis, followed by catalytic hydrogenation of 14·HBr over 10% Pd/C in methanol, yielded the desired 14-methoxydihydromorphinone 15.

Pharmacological Evaluation. Opioid Receptor Binding Assay (ORBA). The 14-methoxy-*N*-methylmorphinanones 3–5, 7, 9, 10, 14, and 15 exhibited a high potency to displace [^{3}H]naloxone from its binding sites in rat brain membranes. The activity of the 14-methoxy derivatives was up to 10 times higher than that of the 14-OH analogues and up to 15 times higher than that of morphine. All compounds of this series exhibited a considerably higher affinity to the [^{3}H]naloxone receptor in the absence of NaCl than in its presence, suggesting high agonist properties. Ratios, calculated from IC_{50} values obtained in the absence vs. presence of NaCl were markedly lower for the compounds 3, 4, 15, and 7 than for morphine or oxymorphone; the other derivatives were in the same range as morphine (3 < 4 < 15 < 7 < 9 < morphine < 5 ≤ oxymorphone ≤ 14 < 10). This suggests a highly preferential agonist profile for all 14-methoxymorphinanones investigated.

The rank order of potency obtained in the binding assay parallels their activity in the behavioral tests. The relatively higher potency of the 4-methoxy and 3,4-dimethoxy derivatives (5 and 10) in the behavioral tests compared to that in the binding assay might refer to favorable pharmacokinetic properties of these derivatives.

Hot-Plate Assay (HPA). The compounds 3–5, 7, 9, 10, and 15 were found to possess extremely high antinociceptive potencies in this test. They exhibited potencies 4–40 times higher than their 14-OH counterparts 3a, 4a, 5a,[4] 7a,[5] 10a[3] ("a" indicates an OH group instead of an OCH_3 group at C-14), and oxymorphone (11). The most potent derivative in this series (15) was about 400 times as potent as morphine after subcutaneous application. The 14-methoxymorphinanones also displayed high potencies when administered orally. Thus, morphinan 10 showed an oral potency in mice about 10 times that of subcutaneously administered morphine and over 60 times that of orally administered morphine.

Nilsen Assay (NA). The results of the NA in mice are in accord with the results obtained by the HPA.

Respiratory Activity (RA). The ability to depress respiration after intravenous injection in rabbits varied over a relative wide range. There were some compounds that induced less respiratory depression than morphine (e.g., 15) but also others that depressed respiration to a greater extent than morphine (e.g., 4, 5, and 10).

Inhibition of Naloxone-Elicited Opioid-Type Withdrawal Jumping (IWJ). The novel compounds were compared with morphine in this test. They prevented naloxone-elicited opioid-type withdrawal jumping in doses that were up to 700 times lower than the ED_{50} of morphine (Table I).

Discussion and Conclusion

The novel 14-methoxy derivatives demonstrate high (similar to morphine) to very high (up to about 400 times more active than morphine) antinociceptive potencies in the HPA and NA. Comparing these 14-methoxymorphinanones with their 14-hydroxy analogues in the HPA and the ORBA, it became apparent that the 14-methoxy group not only increased the affinity for opioid receptors in the binding assay, as previously documented,[2] but also markedly enhanced the antinociceptive potency.

There is a good correlation between the increase in opioid receptor binding affinity and the increase in antinociceptive potency of the 14-methoxymorphinanones compared to the 14-hydroxy derivatives. Discrepancies in the correlation of these parameters in each of the two series, 14-methoxy- and 14-hydroxymorphinanones, certainly might be due to pharmacokinetic differences (e.g., 4 vs. 5 or 4a vs. 5a).

The novel opioid agonists were also found to display other less favorable opioid-type effects, namely, depression of respiration in rabbits and prevention of opioid-type withdrawal behavior in dependent mice.

In conclusion, introduction of a C-14 methoxy group in various morphinan-6-ones results in a series of compounds with extremely high opioid agonist properties. We are presently investigating this group of compounds further in respect to their chemistry and pharmacology.

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 determined by using a JEOL JNM-PMX 60 spectrometer and are reported in parts per million relative to tetramethylsilane as internal reference (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, m = multiplet; *J* (in hertz) = apparent coupling constant). Electron-ionization (EI) and chemical-ionization (CI) mass spectra were obtained from a Finnigan MAT 44S apparatus. Optical rotations (concentration (g/100 mL), solvent) were measured by using a Perkin Elmer 141 polarimeter. Alumina basic (70–230-mesh ASTM) from Merck was used for column chromatography.

(−)-6,7-Didehydro-6,14-dimethoxy-4,5-epoxy-*N*-methylmorphinan (2). A mixture of 1[3] (5.0 g, 17.5 mmol), 60% NaH dispersion in oil (2.1 g, 52.5 mmol), and 100 mL of anhydrous DMF was stirred under a stream of N_2 at room temperature until a clear solution was obtained (ca. 15 min). After cooling to −10 °C, dimethyl sulfate (3.7 ml, 38.9 mmol) was added dropwise during a period of 15 min. The resulting mixture was stirred at −5 to 0 °C for 2 h, poured on 400 mL of ice water, acidified with 2 N HCl, and washed twice with Et_2O. The aqueous layer was rendered alkaline with 30% NH_4OH and extracted several times with a total volume of 400 mL of AcOEt. The organic layer was washed twice with H_2O, dried, and evaporated to give 4.8 g of a crystalline residue which was treated with MeOH to yield 3.65 g (66%) of 2. An analytical sample was prepared by recrystallization from MeOH: mp 200–203 °C; $[\alpha]_D^{23}$ −255.6° (*c* 0.99, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.02 (dd, 1 H, Ar H, *J* = 8, 8 Hz), 6.60 (d, 2 H, Ar H, *J* = 8 Hz), 4.84 (s, 1 H, C-5 H), 4.55 (m, 1 H, C-7 H), 3.52 and 3.27 (2 s, 6 H, OCH_3), 2.40 (s, 3 H, NCH_3); MS (EI), *m/e* 313 (M^+). Anal. ($C_{19}H_{23}NO_3$) C, H, N.

(−)-4,5-Epoxy-14-methoxy-*N*-methylmorphinan-6-one (3). A solution of 2 (3.2 g, 10.2 mmol) in 50 mL of MeOH and 5 mL of concentrated HCl was heated under reflux for 1 h and was then evaporated. The resulting residue was dissolved in H_2O, made alkaline with 30% NH_4OH, and extracted with a total volume of 100 mL of CH_2Cl_2. The organic layer was washed with brine, dried, and evaporated to give a crystalline residue which was

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Table I. Pharmacologial Results of the Novel 14-Methoxy-*N*-methylmorphinan-6-ones Compared with Their 14-Hydroxy Analogues

	ORBA[i] IC_{50},[j] nM			HPA ED_{50}[k]		NA ED_{50}[k]		RA[l]			IWJ[m]
	NaCl	+NaCl	-NaCl/+-NaCl	sc	po	sc	po	dose/kg, μmol iv	% change of vol	% change of rate	ED_{50} sc
3[a]	0.2	16	0.013	0.3 (0.2–0.4)	2.8 (2.0–3.7)	0.3 (0.2–0.4)	4.7 (3.0–6.7)	0.67	–68 (±6.4)	–75 (±5.8)	14.0
3a[a–d]	1.4	16	0.087	1.6 (1.3–1.9)	31 (25–39)						
4[a]	0.02	0.7	0.025	0.5 (0.4–0.7)	1.2 (0.9–1.6)	0.4 (0.3–0.5)	1.0 (0.7–1.4)	0.17	–40 (±12.5)	–32 (±4.6)	2.9
4a[a–d]	0.2	3.4	0.059	2.0 (1.7–2.3)	3.5 (2.5–5.2)						
5[a]	0.3	3.5	0.085	0.06 (0.03–0.1)	1.1 (0.8–1.4)	0.06 (0.05–0.11)	1.6 (1.0–2.5)	0.08	–64 (±5.8)	–66 (±4.0)	2.4
5a[a–d]	0.75	3.7	0.20	0.5 (0.4–0.7)	5.0 (3.7–7.0)						
7[a]	0.2	6	0.033	0.1 (0.09–0.16)	2.2 (1.4–3.5)	0.2 (0.1–0.2)	2.3 (1.5–3.3)	0.18	–48 (±3.0)	–52 (±2.5)	7.0
7a[a,e]	0.3	12	0.025	1.8 (1.3–2.4)		2.0 (1.4–2.8)					
9[a]	0.5	11	0.045	0.8 (0.6–1.0)	2.4 (1.6–3.6)	0.5 (0.4–0.7)	5.4 (3.6–8.2)				
10[a]	0.085	0.85	0.10	0.06 (0.04–0.07)	0.3 (0.2–0.4)	0.05 (0.04–0.07)	0.6 (0.4–0.8)	0.017	–48 (±5.6)	–50 (±3.1)	1.6
10a[a–d]	0.5	1.2	0.42	0.4 (0.3–0.5)		0.3 (0.2–0.4)					
14[f]	0.8	9	0.088	2.7 (2.3–3.3)				0.41	–32 (±2.0)	–38 (±6.8)	5.3
15[f]	0.003	0.08	0.031	0.008 (0.005–0.01)	0.5 (0.4–0.7)	0.02 (0.01–0.02)	0.5 (0.3–0.7)	0.005	–26 (±5.5)	–33 (±7.2)	0.08
11 (oxymorphone)[a]	0.013	0.15	0.086	~0.3	~3.0						
morphine[g]	0.05	0.75	0.066	2.9 (2.5–3.3)	18.9 (14.1–24.9)	4.3 (3.2–6.3)	24.9 (18.0–34.1)	3.3	–38 (±3.3)	–43 (±3.3)	59
naloxone[h]	0.009	0.004	2.57								

[a] Used as base; introduced in diluted HCl solution. [b] The letter "a" indicates a 14-OH group instead of the 14-OCH_3 group. [c] See ref 1. [d] See ref 4. [e] See ref 5. [f] Used as HBr salt; introduced in aqueous solution. [g] Used as sulfate in the HPA and NA, as HCl salt in the ORBA, RA, and IWJ; introduced as aqueous solution. [h] Used as HCl salt; introduced in aqueous solution (IWJ). [i] Opioid receptor binding was performed in rat brain membranes. [j] The IC_{50} value is the concentration required to inhibit the specific [^{3}H]naloxone (1 nM) binding by 50%, in the absence and presence of 150 mM NaCl. [k] The ED_{50} values represent the effective dose at which half of the mice were effected and are in μmol/kg. The numbers in parentheses are 95% standard error limits determined by computerized probit analyses. [l] Respiratory activity in rabbits. The values show the percentage change of the respiratory volume and the change in respiration rate in comparison to the 10-min period prior to the injection. The standard errors of the mean (±SEM) are given in parentheses. [m] Inhibition of naloxone-elicited opioid-type withdrawal jumping in physically dependent mice. ED_{50} values are in μmol/kg.

treated with MeOH to yield 2.3 g (75%) of **3**. Recrystallization from MeOH afforded an analytical sample: mp 172–174 °C; $[\alpha]_D^{23}$ –252.0° (*c* 1.33, $CHCl_3$); IR (KBr) 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.16–6.60 (m, 3 H, Ar H), 4.56 (s, 1 H, C-5 H), 3.28 (s, 3 H, OCH_3), 2.38 (s, 3 H, NCH_3); MS (EI), *m/e* 299 (M^+). Anal. ($C_{18}H_{21}NO_3$) C, H, N.

(–)-4-Hydroxy-14-methoxy-*N*-methylmorphinan-6-one (4). Activated zinc powder (12.0 g, 0.18 mol) was added in portions to a refluxing mixture of **3** (6.0 g, 20.0 mmol), NH_4Cl (12.0 g, 0.22 mol), and 100 mL of MeOH within 5 min. The mixture was refluxed for additional 30 min, filtered, and washed with MeOH, and the filtrate was evaporated. The residue was partitioned between 500 mL of dilute NH_4OH and 200 mL of a mixture of $CHCl_3$/2-propanol (2:1). The aqueous layer was extracted three more times with $CHCl_3$/2-propanol (each time 200 mL). The combined organic extractions were dried and evaporated to afford a crystalline residue which was treated with MeOH to give 5.1 g (84%) of **4**. The analytical sample was obtained by recrystallization from MeOH: mp 253–258 °C dec; $[\alpha]_D^{23}$ –116.8° (*c* 1.43, $CHCl_3$); IR (KBr) 3400 (OH), 1710 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 6.95–6.45 (m, 3 H, Ar H), 3.22 (s, 3 H, OCH_3), 2.26 (s, 3 H, NCH_3); MS (EI), *m/e* 301 (M^+). Anal. ($C_{18}H_{23}NO_3$·0.5MeOH) C, H, N.

(–)-4,14-Dimethoxy-*N*-methylmorphinan-6-one (5). A mixture of **4** (6.0 g, 19.9 mmol), anhydrous K_2CO_3 (8 g, 57.9 mmol), phenyltrimethylammonium chloride (6.8 g, 39.6 mmol), and 100 mL of anhydrous DMF was stirred at 80 °C (bath temperature) under a nitrogen atmosphere for 2 h. The inorganic solid was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The residue was dissolved in CH_2Cl_2, washed with 2 N NaOH and brine, dried, and evaporated to give 5.8 g of a crystalline residue which was treated with MeOH to yield 4.6 g (73%) of **5**. An analytical sample was prepared by recrystallization from MeOH: mp 180–183 °C; $[\alpha]_D^{23}$ –63.3° (*c* 0.81, $CHCl_3$); IR (KBr) 3400 (OH), 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.02 (dd, 1 H, Ar H, *J* = 8, 8 Hz), 6.62 (d, 2 H, Ar H, *J* = 8 Hz), 3.76 (s, 3 H, C-4 OCH_3), 3.30 (s, 3 H, C-14 OCH_3), 2.33 (s, 3 H, NCH_3); MS (EI), *m/e* 315 (M^+). Anal. ($C_{19}H_{25}NO_3$·0.5MeOH) C, H, N.

(–)-14-Methoxy-*N*-methyl-4-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]morphinan-6-one (6). A mixture of **4** (600 mg, 1.99 mmol), anhydrous K_2CO_3 (500 mg, 3.62 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (377 mg, 2.09 mmol), and 10 mL of anhydrous DMF was stirred at room temperature under N_2 for 20 h. After filtration, the filtrate was evaporated and the residue dissolved in CH_2Cl_2, washed with H_2O, dried, and evaporated to give 880 mg of an oil which was crystallized with AcOEt to afford 720 mg (81%) of **6**. An analytical sample was obtained by recrystallization from AcOEt: mp 171–174 °C; $[\alpha]^{23}_D$ –20.9° (*c* 1.01, $CHCl_3$); IR (KBr) 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.00–7.04 (m, 8 H, Ar H), 3.35 (s, 3 H, OCH_3), 2.38 (s, 3 H, NCH_3); MS (CI), *m/e* 446 ($M^+ + 1$). Anal. ($C_{25}N_{27}N_5O_3$) C, H, N.

(–)-14-Methoxy-*N*-methylmorphinan-6-one (7). A mixture of **6** (600 mg, 1.35 mmol), 10% Pd/C catalyst (800 mg), and 10 mL of glacial AcOH was hydrogenated at room temperature and atmospheric pressure for 8 days. The catalyst was filtered off and washed with glacial AcOH, and the filtrate was evaporated. The residue was made alkaline with 30% NH_4OH and extracted three times with a total volume of 30 mL of Et_2O. The organic layer was dried and evaporated to give 270 mg of a crystalline residue which was recrystallized with MeOH to yield 210 mg (55%) of **7**: 243–246 °C dec; $[\alpha]^{23}_D$ –116.8° (*c* 0.94, $CHCl_3$); IR (KBr) 1710 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.15–6.96 (m, 4 H, Ar H), 3.32 (s, 3 H, OCH_3), 2.36 (s, 3 H, NCH_3); MS (CI), *m/e* 286 ($M^+ + 1$). Anal. ($C_{18}H_{23}NO_2$) C, H, N.

(–)-3,14-Dimethoxy-4-hydroxy-*N*-methylmorphinan-6-one (6).[6] Activated zinc powder (21.0 g, 0.32 mol) was added in portions to a refluxing mixture of (–)-14-methoxy-7,8-dihydrocodeinone (**11**)[2,6] (12.0 g, 36.3 mmol), NH_4Cl (21.0 g, 0.4 mol), and 200 mL of MeOH within 5 min. This mixture was refluxed for an additional 20 min and the inorganic solid filtered off, washed with MeOH, and evaporated. The residue was dissolved in 600 mL of H_2O, rendered alkaline with 50 mL of 30% NH_4OH, and extracted several times with a total volume of 300 mL of $CHCl_3$/2-propanol (2:1). The organic phase was dried and evaporated to yield 11.4 g of a foam which was crystallized with MeOH to give 8.8 g (66%) of **9**. Recrystallization of a portion

of this material from MeOH provided an analytical sample of 9:[9] mp 186–188 °C; $[\alpha]^{23}_D$ −70.9° (c 0.81, $CHCl_3$); IR (KBr) 3550 (OH), 1690 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.74 (s, 2 H, Ar H), 3.76 (s, 3 H, C-3 OCH_3), 3.28 (s, 3 H, C-14 OCH_3), 2.36 (s, 3 H, NCH_3); MS (CI), m/e 332 (M^+ + 1). Anal. ($C_{19}H_{25}NO_4$·MeOH) C, H, N.

(−)-3,4,14-Trimethoxy-*N*-methylmorphinan-6-one (10). A mixture of 9 (8.6 g, 25.9 mmol), anhydrous K_2CO_3 (12.0 g, 86.7 mmol), phenyltrimethylammonium chloride (13.5 g, 78.4 mmol), and 120 mL of anhydrous DMF was stirred at 80 °C (bath temperature) under N_2 for 5 h. The inorganic solid was filtered off and washed with CH_2Cl_2, and the filtrate was evaporated. The residue was dissolved in diluted AcOH and the pH was adjusted to 5 with diluted NH_4OH. After two washings with cyclohexane, the aqueous layer was made alkaline with 5 N NaOH and extracted with CH_2Cl_2. The organic phase was washed with brine, dried, and evaporated to give 8.4 g of a brown oil which was crystallized with MeOH to yield 7.3 g (85%) of 10. An analytical sample was obtained by recrystallization from MeOH: mp 106–107 °C; $[\alpha]^{23}_D$ −69.1° (c 0.87, $CHCl_3$); IR (KBr) 1700 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.70 (s, 2 H, Ar H), 3.88 and 3.74 (2 s, 6 H, C-3,4 OCH_3), 3.32 (s, 3 H, C-14 OCH_3), 2.33 (s, 3 H, NCH_3); MS (CI), m/e 346 (M^+ + 1). Anal. ($C_{20}H_{27}NO_4$·0.5MeOH) C, H, N.

(−)-3-(Benzyloxy)-4,5-epoxy-14-hydroxy-*N*-methylmorphinan-6-one (12).[8] A mixture of oxymorphone (11) (2.0 g, 6.64 mmol), anhydrous K_2CO_3 (2.0 g, 14.5 mmol), benzyl bromide 0.87 mL, 7.31 mmol), and 20 mL of anhydrous DMF was stirred at room temperature under N_2 for 20 h. After filtration and evaporation of the filtrate, the remaining oil was acidified with 2 N HCl, washed twice with Et_2O, and alkalized with 30% NH_4OH. Extraction with CH_2Cl_2, followed by washings with H_2O and brine, drying, and evaporation afforded 2.6 g of an oil which was crystallized with MeOH to yield 2.15 g (83%) of 12: mp 131–133 °C [lit.[8] mp 135.5–136.5 °C ($CHCl_3$/EtOH)].

(−)-3-(Benzyloxy)-6,7-didehydro-6,14-dimethoxy-4,5-epoxy-*N*-methylmorphinan (13). A mixture of 12 (1.8 g, 4.60 mmol), 60% NaH dispersion in oil (610 mg, 15.25 mmol), and 10 mL of anhydrous DMF was stirred under a stream of N_2 at room temperature until a clear solution was obtained (ca. 30 min). After the mixture cooled to 0 °C, dimethyl sulfate (0.95 mL, 10.04 mmol) was added at once. This mixture was stirred at 0 °C for 30 min and then at room temperature for another 30 min, poured on 100 mL of ice water, acidified with 2 N HCl, and washed twice with Et_2O. The aqueous layer was made alkaline with 30% NH_4OH and extracted with CH_2Cl_2, and the organic phase was washed twice with H_2O, dried, and evaporated to give 1.8 g of a crystalline residue which was treated with MeOH to yield 1.55 g (80%) of 13. Recrystallization of a portion of this material gave analytically pure 13: mp 202–206 °C; $[\alpha]^{23}_D$ −132.6° (c 1.41, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 7.22 (m, 5 H, Ar H), 6.66 (d, 1 H, Ar H, J = 8 Hz), 6.44 (d, 2 H, Ar H, J = 8 Hz), 5.12 (s, 2 H, OCH_2), 4.85 (s, 1 H, C-5 H), 4.53 (m, 1 H, C-7 H), 3.48 and 3.24 (2 s, 6 H, OCH_3), 2.34 (s, 3 H, NCH_3); MS (CI), m/e 420 (M^+ + 1). Anal. ($C_{26}H_{29}NO_4$) C, H, N.

(−)-3-(Benzyloxy)-4,5-epoxy-14-methoxy-*N*-methylmorphinan-6-one Hydrobromide (14). A solution of 13 (1.2 g, 2.86 mmol) in 20 mL of MeOH and 2 mL of concentrated HCl was heated under reflux for 1.5 h. After evaporation, the residue was basified with 30% NH_4OH and extracted with CH_2Cl_2, and the organic layer was washed with brine, dried, and evaporated to afford 1.05 g of a foam. This foam was converted into the hydrobromide salt 14 (950 mg, 68%) in the usual manner. Recrystallization from MeOH/Et_2O gave an analytical sample: mp 247–250 °C; $[\alpha]^{23}_D$ −133.4° (c 1.1, DMF); IR (KBr) 3420 ($^+$NH), 1720 (CO) cm^{-1}; ^1H NMR ($CDCl_3$) δ 9.90 (br s, 1 H, $^+$NH), 7.30 (m, 5 H, Ar H), 6.80 (d, 2 H, Ar H, J = 8 Hz), 6.62 (d, 2 H, Ar H, J = 8 Hz), 5.18 (s, 2 H, OCH_2), 4.72 (s, 1 H, C-5 H), 3.58 (s, 3 H, OCH_3), 3.08 (s, 3 H, $^+NCH_3$); MS (CI), m/e 406 (M^+ + 1). Anal. ($C_{25}H_{27}NO_4$·HBr) C, H, N.

(−)-4,5-Epoxy-3-hydroxy-14-methoxy-*N*-methylmorphinan-6-one Hydrobromide (15). A mixture of 14 (500 mg, 1.03 mmol), 10% Pd/C catalyst (150 mg), and 40 mL of MeOH was hydrogenated at room temperature and 45 psi for 16 h. The catalyst was filtered off and washed with MeOH, and the filtrate was evaporated to yield 400 mg of a crystalline residue which was recrystallized from MeOH to give 370 mg (91%) of analytically pure 15: mp >300 °C dec; $[\alpha]^{23}_D$ −171.7° (c 1.28, DMF); IR (KBr) 3420 and 3200 (OH, $^+$NH), 1715 (CO) cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 9.33 and 9.00 (2 s, br, OH, $^+$NH), 6.58 (s, 2 H, Ar H), 4.88 (s, 1 H, C-5 H), 3.38 (s, 3 H, OCH_3), 2.90 (d, 3 H, $^+NCH_3$, J = 4 Hz); MS (CI), m/e 316 (M^+ + 1). Anal. ($C_{18}H_{21}NO_4$·HBr) C, H, N, Br.

Pharmacology. Methods. Opioid Receptor Binding Assay (ORBA). Receptor binding was performed on crude rat brain membranes,[10,11] which had been washed five times by homogenizing in 50 mM Tris-HCl buffer, pH 7.2, and centrifuging (15000*g*, × 10 min). The incubation was performed in 50 mM Tris buffer (final volume 500 μL) containing membranes (about 1 mg of protein), [^{3}H]naloxone (1 nM, NEN, 51 Ci/mMol), and various concentrations of the compound to be tested. Binding was evaluated in the absence and in the presence of 150 mM NaCl. Nonspecific binding was determined in the presence of 3 and 30 μM oxymorphone for incubations in the absence and presence of NaCl, respectively. The samples were incubated at 0 °C for 90 min and then passed rapidly through Whatman GF/B glass fiber filters. The radioactivity trapped on the filters was measured by liquid scintillation counting. Drug concentrations resulting in a 50% inhibition of [^{3}H]naloxone binding (IC_{50} values) were determined by regression analysis.

Hot-Plate Assay (HPA). The HPA was carried out in mice as previously described.[12–14]

Nilsen Assay (NA). This test was performed essentially as described.[15]

Respiratory Activity (RA). Four conscious rabbits (strain Burgundian, stock Füllinsdorf) with a body weight of 2.2–3.1 kg were used per dose. The animals were mechanically immobilized (with the head fixed) in a box with background music and mild light. A mask was tightly attached to the snout. The respiration rate was assessed by using a pressure transducer fitted to the mask. The volume of air exhaled was measured with a gas meter. Both respiration rate and respiratory minute volume were recorded continuously. After regular respiration had been maintained for at least 10 min, the solutions (1.5 mL/kg) were injected slowly into an ear vein and respiration rate and respiratory volume were recorded over a further 15-min period. Drug-induced mean alterations from the third to the 12th min after intravenous injection are expressed as a percentage of the mean values obtained during the 10-min period prior to the injection. The animals were retested three to four times with a recovery phase of at least 7 days between separate experiments.

Inhibition of Naloxone-Elicited Opioid-Type Withdrawal Jumping (IWJ).[16] Male mice (strain Füllinsdorf-Albino SPF, 23–30-g body weight) were made physically dependent on morphine by implanting a pellet containing 75 mg of the opioid under the skin of the neck. Withdrawal jumping was elicited about 72 h after implantation by injecting the opioid antagonist naloxone (0.1 mg/kg, sc). A mean number of jumps of >150/20 min was observed in 16 animals (control group). Sixty minutes before naloxone injection, the test compounds were administered subcutaneously to eight animals per dosage group. Measurement of withdrawal jumps was made by placing the animals singly on

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a platform at the bottom of a plexiglas cylinder (height 35 cm, inner diameter 14.5 cm), where the number of jumps could be counted electromechanically for 20 min. The ED_{50} for inhibition of opioid-type withdrawal jumping was determined from a cubic spline curve and represents the dose that reduced the number of jumps by 50% compared to the control group.

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Registry No. 1, 81165-08-4; 2, 92055-56-6; 3, 92055-57-7; 4, 92055-58-8; 5, 92055-59-9; 6, 92055-60-2; 7, 92055-61-3; 8, 38252-28-7; 9, 78072-08-9; 10, 92055-62-4; 11, 76-41-5; 12, 5868-03-1; 13, 92055-63-5; 14, 92055-64-6; 15, 92078-30-3; 5-chloro-1-phenyl-1*H*-tetrazole, 14210-25-4; benzyl bromide, 100-39-0.

[(Aminomethyl)aryloxy]acetic Acid Esters. A New Class of High-Ceiling Diuretics. 1. Effects of Nitrogen and Aromatic Nuclear Substitution[1]

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A series of Mannich bases and aminomethyl derivatives of ethyl [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetate were synthesized and tested for saluretic and diuretic activities. The effects of nitrogen and aromatic nuclear substitution, reorientation of the aminomethyl group relative to that of the phenolic hydroxyl group, and replacement of either the phenolic hydroxyl or the aminomethyl group by other functional groups are described. Ethyl [2,3-dichloro-4-[3-(aminomethyl)-4-hydroxybenzoyl]phenoxy]acetate (**27**) was found to be a very potent, high-ceiling diuretic.

In the search for nonsulfonamide diuretics in our laboratories, we discovered that [2,3-dichloro-4-(4-hydroxybenzoyl)phenoxy]acetic acid I is a low-ceiling, uricosuric agent.[2] In much earlier work, we found a series of bis-Mannich bases of alkyl-substituted phenol, exemplified by II, to display diuretic activity in animal tests.[3] Recently a series of papers reporting the diuretic activity of 2-(aminomethyl)phenols has appeared.[4-6] In an effort to enhance the potency and modify the pharmacological profile of I, we prepared the Mannich bases of I and observed that the ethyl ester of bis(dimethylamino)methyl derivative **17** is a potent, high-ceiling diuretic. This led

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