# 253. Structure-Activity Relationship of Oxygenated Morphinans. V. Narcotic Agonist and Antagonist Activity in the 14-Hydroxymorphinan Series

Preliminary Communication

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*Summary*

The synthesis of several 14-hydroxymorphinans, using oxymorphone (=3,14-dihydroxy-4,5-epoxy-*N*-methylmorphinan-6-one, **1**) as starting material, is described. The antinociceptive potency of the *N*-methyl substituted 14-hydroxymorphinans was determined. Thus, in order of antinociceptive potency, 14-hydroxy-4-methoxy-*N*-methylmorphinan-6-one (**5**) > 4,5-epoxy-14-hydroxy-*N*-methylmorphinan-6-one (**3**) > 4,14-dihydroxy-*N*-methylmorphinan-6-one (**4**) > 14-hydroxy-4-methoxy-*N*-methylmorphinan (**11**) ≈ 4,14-dihydroxy-*N*-methylmorphinan (**12**). The most potent compound in this series, 14-hydroxy-4-methoxy-*N*-methylmorphinan-6-one (**5**), was found to have about six times the potency of morphine; it was equipotent with levorphanol.

The high antinociceptive potency of 4-methoxy-*N*-methylmorphinan-6-one, prepared from 3-deoxydihydromorphine of the natural series of opioids [1], and 3,4-dimethoxy-*N*-methylmorphinan, prepared from natural thebaine [2], was recently reported. This program was extended to include the preparation of congeners with *N*-substituents known to afford narcotic antagonists [3], and of highly potent morphinan-6-ones unsubstituted in the aromatic ring moiety [4]. The events leading to these developments were recently summarized [5] [6]. We now would like to report on the synthesis (s. *Scheme*) and biological properties of representative morphinans containing a 14-hydroxy substituent. This extension was stimulated by the proven clinical effectiveness of butorphanol as an analgesic [7], by the finding of oxilorphan as a strong narcotic antagonist [7], and by the discovery of long-acting opiate agonists and antagonists among 14-hydroxydihydromorphinone hydrazones [8].

The tetrazolyloxy compound **2**[2]) was obtained from oxymorphone (**1**) by alkylation with 5-chloro-1-phenyl-1*H*-tetrazole in DMF in the presence of $K_2CO_3$

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[2]) All new compounds were characterized by elemental analysis and show the expected spectroscopic features.

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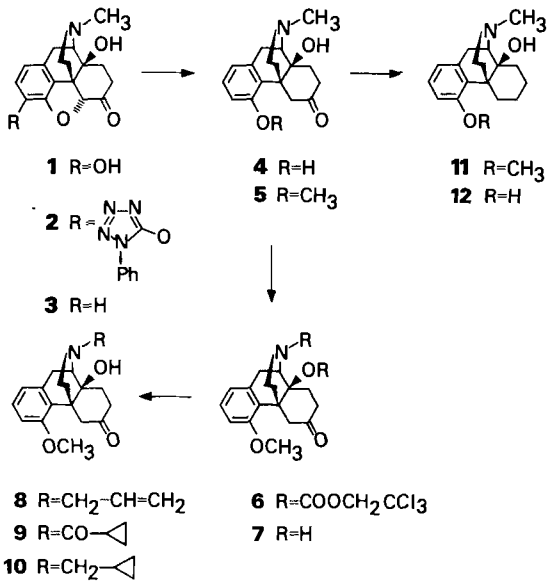


in 91% yield, m.p. 99–102°[3]) (ethyl acetate), $[\alpha]_D^{26} = -179.0°$[4]) ($c = 0.83$, $CHCl_3$) [IR.[5]) (KBr): 3400 and 3315 (OH), 1730 (C=O). – $^1$H-NMR.[6]) ($CDCl_3$): 7.84 (*m*, 2 H, arom. H); 7.52 (*m*, 3 H, arom. H); 7.14 (*d*, 1 H, arom. H, $J = 8$); 6.72 (*d*, 1 H, arom. H, $J = 8$); 4.68 (*s*, 1 H, H–C(5)); 2.40 (*s*, 3 H, $H_3C$–N). – MS.[7]): 445 ($M^+$)].

Hydrogenation of **2** in glacial acetic acid at 65° with Pd/C as catalyst gave the epoxy ketone **3** in 70% yield, m.p. 223–225°, $[\alpha]_D^{26} = -267.6°$ ($c = 0.96$, $CHCl_3$) [IR. (KBr): 3375 (OH), 1730 (C=O). – $^1$H-NMR. ($CDCl_3$): 7.08 (*d*×*d*, 1 H, $J = 8$, and 8, arom. H); 6.75 (*d*, 1 H, $J = 8$, arom. H); 6.70 (*d*, 1 H, $J = 8$, arom. H); 4,63 (*s*, 1 H, H–C(5)); 2.42 (*s*, 3 H, $H_3C$–N). – MS.: 285 ($M^+$)].

Cleavage of the O-bridge of **3** with activated Zn and ammonium chloride in refluxing ethanol afforded the dihydroxy ketone **4** in 62% yield, m.p. 233–236° (2-propanol), $[\alpha]_D^{26} = -149.3°$ ($c = 0.90$, $CHCl_3$) [IR. (KBr): 3280 br. (OH), 1710 (C=O). – $^1$H-NMR. ($CDCl_3$): 6.92 (*d*×*d*, 1 H, arom. H, $J = 8$, and 8); 6.76 (*d*, 1 H, $J = 8$, arom. H); 6.56 (*d*, 1 H, $J = 8$, arom. H); 4.11 (*d*, 1 H, $J = 14$, $H_\beta$–C(5)); 2.34 (*s*, 3 H, $H_3C$–N). – MS.: 287 ($M^+$)].

Alkylation of the phenolic hydroxyl group of **4** with phenyltrimethylammonium chloride in DMF in the presence of $K_2CO_3$ gave the methoxy ketone **5** in 77% yield, m.p. 191–193° (ethanol), $[\alpha]_D^{26} = -83.9°$ ($c = 0.88$, $CHCl_3$) [IR. (KBr): 3440 (OH), 1705 (C=O). – $^1$H-NMR. ($CDCl_3$): 7.04 (*d*×*d*, 1 H, $J = 8$, and 8, arom. H); 6,65

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3) Melting points are corrected.
4) Optical rotations (concentration (g/100 ml), solvent).
5) IR. spectra: $\tilde{\nu}_{max}$ in $cm^{-1}$.
6) $^1$H-NMR. spectra: at 100 MHz; internal standard tetramethylsilane ($\delta = 0.0$ ppm); *s* = singlet, *d* = doublet, *d*×*d* = doublet of doublets, *t* = triplet, *m* = multiplet; *J* = spin-spin coupling constant.
7) MS. spectra (*m/z*): electron ionization at 70 eV.

(*d*, 2 H, $J=8$, arom. H); 4.54 (*s*, 1 H, OH); 3.79 (*s*, 3 H, $CH_3O$); 2.33 (*s*, 3 H, $H_3C-N$). – MS.: 301 ($M^+$)].

Treatment of **5** with excess 2,2,2-trichloroethyl chloroformate in chloroform in the presence of $KHCO_3$ yielded the ester carbamate **6** in 85% yield, m.p. 115–116° (THF), $[\alpha]_D^{26} = -111.4°$ ($c=0.93$, $CHCl_3$) [IR. (KBr): 1765 (ester), 1710 (C=O). – $^1$H-NMR. ($CDCl_3$): 7.14 (*d*×*d*, 1 H, $J=8$, and 8, arom. H); 6.72 (*d*, 1 H, $J=8$, arom. H); 6.68 (*d*, 1 H, $J=8$, arom. H); 5.52 (*t*, 1 H, $J=5$, H–C(9)); 5.00–4.50 (*m*, 4 H, 2 $CH_2CCl_3$); 3.84 (*s*, 3 H, $CH_3O$). – MS. (CI.-$NH_3$): 655, 657 ($M^+$)].

The key intermediate for the antagonist series, (–)-14-hydroxy-4-methoxymorphinan-6-one (**7**), was formed by treatment of **6** with activated Zn and ammonium chloride in refluxing ethanol in 68% yield, m.p. 137–139° (ethyl acetate), $[\alpha]_D^{26} = -66.5°$ ($c=1.09$, $CHCl_3$) [IR. (KBr): 3400, 3350, 3330 and 3310 (OH and NH), 1705 (C=O). – $^1$H-NMR. ($CDCl_3$): 7.05 (*d*×*d*, 1 H, $J=8$, and 8, arom. H); 6.65 (*d*, 1 H, $J=8$, arom. H); 3.80 (*s*, 3 H, $CH_3O$). – MS.: 287 ($M^+$)].

*N*-Allylation of **7** with allylbromide in DMF in the presence of $K_2CO_3$ afforded (–)-*N*-allyl-14-hydroxy-4-methoxymorphinan-6-one (**8**) in 78% yield, m.p. 166–167° (ethanol), $[\alpha]_D^{26} = -112.8°$ ($c=0.90$, $CHCl_3$) [IR. (KBr): 3420 (OH), 1710 (C=O). – $^1$H-NMR. ($CDCl_3$): 7.04 (*d*×*d*, 1 H, $J=8$, and 8, arom. H); 6.64 (*d*, 2 H, $J=8$, arom. H); 5.70 (*m*, 1 H, =CH); 5.14 (*m*, 2 H, $=CH_2$); 4.54 (*s*, 1 H, OH); 3.80 (*s*, 3 H, $OCH_3$). – MS.: 327 ($M^+$)].

Acylation of **7** with cyclopropylcarbonyl chloride in DMF in the presence of $K_2CO_3$ gave the amide **9** in 86% yield, m.p. 223–225° (ethanol), $[\alpha]_D^{26} = -167.2°$ ($c=0.97$, $CHCl_3$) [IR. (KBr): 3280 br. (OH), 1715 (C=O), 1665 and 1610 (amide). – $^1$H-NMR. ($CDCl_3$): 7.09 (*d*×*d*, 1 H, $J=8$, and 8, arom. H); 6.68 (*d*, 1 H, $J=8$, arom. H); 6.64 (*d*, 1 H, $J=8$, arom. H); 4.90 (*m*, 1 H, H–C(9)); 3.82 (*s*, 3 H, $CH_3O$). – MS.: 355 ($M^+$)]. Reduction of **9** with $LiAlH_4$ in diethyl ether, followed by *Oppenauer* oxidation of the crude mixture of alcohols with potassium *t*-butoxide and benzophenone in toluene afforded (–)-*N*-cyclopropylmethyl-14-hydroxy-4-methoxymorphinan-6-one (**10**) in 71% yield, m.p. 134–136° (diisopropyl ether), $[\alpha]_D^{25} = -108.6°$ ($c=0.80$, $CHCl_3$). – IR. (KBr): 3440 (OH), 1710 (C=O). – $^1$H-NMR. ($CDCl_3$): 7.04 (*d*×*d*, 1 H, $J=8$, and 8, arom. H); 6.64 (*d*, 2 H, $J=8$, arom. H); 4.68 (*s*, 1 H, OH); 3.80 (*s*, 3 H, $CH_3O$). – MS.: 341 ($M^+$)].

*Wolff-Kishner* reduction of **5**, using hydrazine hydrate in triethylene glycol, gave a mixture of the methoxymorphinan **11** and the dihydroxymorphinan **12**. This mixture was separated by chromatography on alumina (grade III, elution with $CH_2Cl_2$), to yield 40% of **11** [M.p. 80.5–81.5° (methanol), $[\alpha]_D^{23} = -38.4°$ ($c=1.07$, $CHCl_3$). – IR. (KBr): 3450 and 3400 (OH). – $^1$H-NMR. ($CDCl_3$): 7.08 (*d*×*d*, 1 H, $J=8$, and 8, arom. H); 6.68 (*d*, 1 H, $J=8$, arom. H); 6.64 (*d*, 1 H, $J=8$, arom. H); 4.34 (*s*, 1 H, OH); 3.76 (*s*, 3 H, $CH_3O$); 2.32 (*s*, 3 H, $H_3C-N$). – MS.: 287 ($M^+$)] and 26% of **12** [M.p. 255–257° (dec.) (methanol), $[\alpha]_D^{23} = -60.2°$ ($c=0.90$, DMSO). – IR. (KBr): 3250 br. (OH). – $^1$H-NMR. ($D_6$-DMSO): 8.98 (*s*, 1 H, OH); 6.82 (*d*×*d*, 1 H, $J=8$, and 8, arom. H); 6.49 (*d*, 2 H, $J=8$, arom. H); 4.08 (*s*, 1 H, OH); 2.12 (*s*, 3 H, $H_3C-N$). – MS.: 273 ($M^+$)].

The 14-hydroxy-4-methoxy-*N*-methylmorphinan-6-one (**5**) was found to be remarkably potent as an antinociceptive *(Table)*. This aromatic methyl ether was

Table. *Antinociceptive Activity of the 14-Hydroxy-N-methylmorphinans*

| Compound | $ED_{50}$[a]) | Compound | $ED_{50}$[a]) |
|---|---|---|---|
| **3** | 1.6 (1.3–1.9) | **12** | 3.0 (2.2–4.2) |
| **4** | 2.0 (1.7–2.3) | Morphine sulfate | 2.9 (2.5–3.3) |
| **5** | 0.5 (0.4–0.7) | Levorphanol tartrate | 0.5 (0.2–0.7) |
| **11** | 3.1 (2.3–4.3) | | |

[a]) Antinociceptive activity determined by hot plate assay, s.c. injection [10] [11] [12]. The $ED_{50}$, the effective dose at which half the mice are effected, values are in μmol/kg. The parenthesized numbers are 95% standard error limits determined by computerized probit analysis. The bases were introduced in dilute HCl-solution, the salts in aqueous solution.

found to be four times more potent than the comparable phenolic compound (**4**). We have found similar potency differences between phenols and corresponding methyl ethers in non-14-hydroxylated morphinans [1] [9]. In each case, in contradistinction to C(3)-substituted opiates, the C(4)-ether was more potent than the C(4)-phenol. The ether **5** is the most potent antinociceptive which we have found, thus far, in this series. It is equipotent with levorphanol, and about six times as potent as morphine. Thus, the 4-methoxymorphinans continue to defy prediction; the activity of these opioid aromatic ethers could not have been anticipated from any known structure-activity theory. The narcotic antagonist activity of compound **8** and **10** are presently under investigation and the results will be reported elsewhere.

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