191. Synthesis, Structure Elucidation, and Pharmacological Evaluation of 5-Methyl-oxymorphone (= 4,5α-Epoxy-3,14-dihydroxy-5,17-dimethylmorphinan-6-one)

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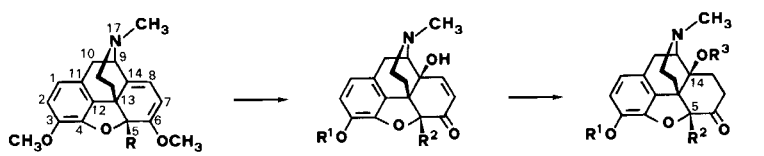
Synthesis of 5-methyl-oxymorphone (**3**) was accomplished by oxidation of 5-methylthebaine (**4**) with performic acid, followed by catalytic hydrogenation and cleavage of the 3-MeO group. X-Ray analysis confirmed that the 14-OH group has, like the one in oxymorphone (**1**), β-orientation. Pharmacological studies *in vivo* and *in vitro* showed **3** to possess slightly less opioid agonistic properties than **1**.

In our pursuit of structure-activity relationships in the *N*-methylmorphinan-6-one series, we have found that 14-*O*-methylation of oxymorphone (= 4,5α-epoxy-3,14-dihydroxy-17-methylmorphinan-6-one; **1**) results in a compound (**2**) which possesses much higher antinociceptive potency and opioid receptor binding affinity than the parent compound of the series, oxymorphone (**1**). It was of interest to determine if a 5-Me group on **1** would enhance the opioid agonistic properties to a similar extent as the 14-*O*-Me group. In addition, the up to now unknown structure of 5-methyl-oxymorphone (**3**) would be a starting point for further synthetic and pharmacologic investigations in the class of 14-hydroxy-morphinan-6-ones.



4 R = CH_3
5 R = H

6 $R^1 = R^2 = CH_3$
7 $R^1 = CH_3$, $R^2 = H$

1 $R^1 = R^2 = R^3 = H$
2 $R^1 = R^2 = H$, $R^3 = CH_3$
3 $R^1 = R^3 = H$, $R^2 = CH_3$
8 $R^1 = R^2 = CH_3$, $R^3 = H$

Chemistry. – The oxidation of 5-methylthebaine (**4**) [2] [3] with *m*-chloroperbenzoic acid in $AcOH/CF_3COOH$, carried out as described for the oxidation of thebaine (**5**) to 14-hydroxycodeinone (**7**) [4], was unsuccessful; and likewise, the oxidation with performic acid employing the conditions of a published procedure [5]. However, we found that the oxidation of 5-methylthebaine (**4**) with performic acid proceeded smoothly at lower temperatures and prolonged reaction time (4° and 66 h instead at 40° and 6.5 h [5])

affording 14-hydroxy-5-methylcodeinone (**6**) in 84% yield[1]). On catalytic hydrogenation of **6**, followed by 3-*O*-demethylation of **8** with 48% HBr solution, 5-methyl-oxymorphone (= 14-hydroxymetopon **3**) was obtained in good yield. We recognized that cleavage of the 3-MeO group with 48% HBr solution gave cleaner products and higher yields in the 5-methyl series in comparison to the 5-unsubstituted series of morphinan-6-ones.

X-Ray analysis of **8** proved β-orientation of the 14-OH group. The novel series, accordingly, has the same configuration as 14-hydroxycodeinone (**7**) and its derivatives.

X-Ray Structure Analysis of 8. – Compound **8** crystallized in the space group $P2_1$, $Z = 4$, with unit-cell dimensions $a = 16.548$ (5) Å, $b = 11.375$ (2) Å, $c = 8.986$ (2) Å, $\beta = 100.06°$. The calculated density was 1.314 $g \cdot cm^{-3}$. A total of 2899 unique reflections with 2 [θ] less than 116.0° were measured on an automated four-circle diffractometer using monochromatic Cu radiation. Reflections with 3 $[\sigma](F) > (F)$ were suppressed and flagged as unobserved. The structure was solved using the random tangent routine (RANT) of the SHELXTL program library (*G. M. Sheldrick*, 1981) and was refined by the least-squares method with anisotropic temperature factors for all atoms except H-atoms. H-Atoms were included with isotropic temperature factors at calculated positions. The final *R* factor was 0.0498 for 2056 observed reflections. The *Figure* shows an ORTEP plot of the molecule, the atomic coordinates, bond lengths, bond angles, and anisotropic temperature factors have been deposited with the *Cambridge Crystallographic Data Center*.

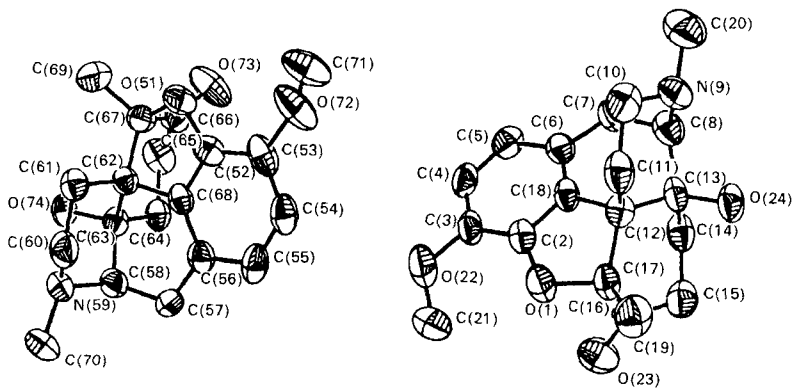


Figure. *ORTEP plot of* **8**. Arbitrary numbering.

Pharmacological Evaluation and Conclusion. – In the AcOH writhing test, 5-methyl-oxymorphone (**3**) injected subcutaneously was found to be slightly less potent than oxymorphone (**1**), and it had only about $^1/_{100}$ the potency of the 14-methoxymorphinanone **2** in this test (see *Table 1*).

In the opioid receptor binding studies, **3** had about $^1/_6$ the affinity of **1** and $^1/_{30}$ the affinity of **2** for the naloxone-labeled μ-receptor binding sites. Similar to **1** and **2**, **3** had only little or no potency in displacing EKC (κ-selective) from its binding sites, suggesting preferential interaction with μ rather than κ receptors (see *Table 2*).

In conclusion, a 5-Me group in oxymorphone (**1**) slightly reduces the opioid agonistic properties of oxymorphone *in vivo* and *in vitro* and does not enhance the μ activity, in contrast to the 14-*O*-methyl group.

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[1]) The oxidation of thebaine (**5**) under the same conditions gave 14-hydroxycodeinone (**7**) in similar yields.

Table 1. *Antinociceptive Potencies*

Compound	ED_{50}[a])
3 · HBr	52 (28–79.7)
8	2910 (955–5650)
2 · HBr	0.48 (0.26–0.75)
Oxymorphone (**1**)	31 (16–50)
Morphine sulfate	389 (94–903)

[a]) The ED_{50} is in μg/kg, s.c. (95% confidence interval). The antinociceptive potencies were determined by the AcOH writhing test [6] [7]. The mouse writhing response was defined as a contraction of the abdominal musculature followed by the extension of the hind limbs. The response was induced by intraperitoneal administration of 0.6% AcOH in a volume of 20 ml/kg. Five CF-1 male mice (Charles River, Portage, MI, USA), weighing approximately 20 g after being fasted overnight, were observed for the writhing responses. The observation period was 10 min in duration, beginning 5 min after AcOH administration. The % inhibition of writhing was calculated from the average number in the appropriate control group (averaging between 35 and 40/10 min period). The dose required to inhibit the average number of writhes by 50% was defined as the ED_{50} and was calculated by a linear regression program, as well as the 95% confidence interval.

Table 2. *Opioid Receptor Binding Affinities*

Compound	[^{3}H]Naloxone[a]) K_i [nM][b])	[^{3}H]EKC[a]) K_i [nM][b])
3 · HBr	41.8	> 1000
8	> 1000	> 1000
2 · HBr	1.37	222.6
Oxymorphone (**1**)	6.60	1537
Morphine sulfate	9.7	167

[a]) [^{3}H]Ethylketocyclazocine ([^{3}H]EKC, κ receptor) binding and [^{3}H]naloxone (μ receptor) binding were determined using a modification of the method of *Werling et al.* [8]. Briefly, crude synaptosomal membranes of guinea-pig cortex and whole rat brain *(minus cerebellum)* were incubated with [^{3}H]EKC and [^{3}H]naloxone, respectively. [^{3}H]EKC incubations also contained 100 nM of fentanyl and [D-Ala^2-D-Leu^5]enkephalin to prevent binding to μ and δ receptors, respectively. Values represent means of triplicate determinations.

[b]) $K_i = IC_{50}/[1 + (L/K_D)]$, where L is ligand concentration and K is the ligand receptor dissociation constant as determined by *Scatchard/Rosenthal* analysis.

Experimental Part

General. Thebaine (**5**) was a gift of *Alkaloida, Chemical Works*, H–4440 Tiszavasvari, Hungary. Oxymorphone (**1**) was purchased from *Diosynth*, Apeldoorn, Holland. Morphine sulfate was from *Lilly Research Laboratories, Eli Lilly and Company*, Indianapolis, IN, USA. [^{1}H]EKC and [^{1}H]naloxone were obtained from *New England Nuclear*, Boston, MA, USA. M.p.: *Kofler* melting point microscope; uncorrected. Optical rotations (concentrations (g/100 ml), solvent): *Perkin-Elmer-141* polarimeter. IR spectra (in cm^{-1}): *Beckman AccuLab 2* apparatus. ^{1}H-NMR spectra: *Jeol-JNM-PMX-60* spectrometer; in ppm to tetramethylsilane as internal reference.

14-Hydroxy-5-methylcodeinone (= *7,8-Didehydro-4,5α-epoxy-14-hydroxy-3-methoxy-5,17-dimethylmorphinan-6-one;* **6**). Ice-cold 0.7% H_2SO_4 (41 ml), 88% HCO_2H (13 ml), and 30% H_2O_2 soln. (26 ml) were added to 5-methylthebaine (**4**; 30 g, 92.2 mmol) [2] [3]. This mixture was stirred at 0° until a clear soln. was obtained (*ca.* 20 min). This soln. was kept in the refrigerator (4°) for 66 h, poured on *ca.* 200 ml ice-water, alkalinized with conc. NH_4OH soln. and extracted with $CHCl_3$ (1 × 150 ml, 2 × 50 ml). The org. layer was dried and evaporated to give 30.07 g of a slightly brown crystalline residue which was treated with 20 ml of boiling EtOH to yield 23.98 g of **6**. Another 1.40 g were obtained from the mother liquor. Total: 25.38 g (84%). A portion of this material was

recrystallized from EtOH for analysis. M.p. 184–186°. $[\alpha]_D^{20} = -137.0$ ($c = 0.88$, $CHCl_3$). IR (KBr): 3380 (OH), 1675 (C=O). ^{1}H-NMR ($CDCl_3$): 6.55 (*dd*, $J = 8, 8, 2$ arom. H); 6.52 (*d*, $J = 10$, 1 olef. H); 6.04 (*d*, $J = 10$, 1 olef. H); 3.80 (*s*, MeO); 2.40 (*s*, MeN); 1.66 (*s*, Me–C(5)). Anal. calc. for $C_{19}H_{21}NO_4$ (327.38): C 69.71, H 6.47, N 4.28; found: C 69.42, H 6.63, N 4.22.

5-Methyl-oxycodone (= *4,5α-Epoxy-14-hydroxy-3-methoxy-5,17-dimethylmorphinan-6-one*; **8**). A mixture of **6** (8.0 g, 24.44 mmol), 10% Pd/C (800 mg), and EtOH (200 ml) was hydrogenated at r.t. and 30 psi for 1 h. After filtration, the filtrate was evaporated to give 8.06 g of a colorless, crystalline solid which was recrystallized from 6 ml of EtOH to yield 6.64 g of **8**. Another 1.43 g were obtained from the mother liquor. Total: 7.31 g (91%). Recrystallization of a portion of this material gave an anal. sample. M.p. 144–145°. $[\alpha]_D^{20} = -170.4$ ($c = 1.09$, $CHCl_3$). IR (KBr): 3380 (OH), 1710 (C=O). ^{1}H-NMR ($CDCl_3$): 6.55 (*dd*, $J = 8, 8, 2$ arom. H); 3.83 (*s*, MeO); 2.37 (*s*, MeN); 1.63 (*s*, Me–C(5)). Anal. calc. for $C_{19}H_{23}NO_4$ (329.40): C 69.28, H 7.04, N 4.25; found: C 69.25, H 7.20, N 4.21.

5-Methyl-oxymorphone Hydrobromide (= *4,5α-Epoxy-3,14-dihydroxy-5,17-dimethylmorphinan-6-one Hydrobromide*; **3** · HBr). A mixture of **8** (1.5 g, 4.55 mmol) in 48% HBr soln. (5 ml) was refluxed for 15 min. Evaporation afforded a slightly pink foam which was crystallized from 2 ml of MeOH to give 1.68 g (90%) of **3**. Anal. pure material was obtained by recrystallization from MeOH (1.12 g). M.p. 287–291° (dec.). $[\alpha]_D^{20} = -102.1$ ($c = 1.06$, H_2O). IR (KBr): 3400 (NH^+, OH), 1710 (C=O). ^{1}H-NMR ((D_6)DMSO): 9.17, 6.12 (2*s*, 2 OH, NH^+); 6.56 (*s*, 2 arom. H); 2.85 (*s*, MeN^+), 1.50 (*s*, Me–C(5)). Anal. calc. for $C_{18}H_{21}NO_4 \cdot HBr \cdot 0.5$ MeOH (412.30): C 53.89, H 5.87, N 3.40, Br 19.38; found: C 53.66, H 6.00, N 3.34, Br 19.25.

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REFERENCES

[1] H. Schmidhammer, L. Aeppli, L. Atwell, F. Fritsch, A. E. Jacobson, M. Nebuchla, G. Sperk, *J. Med. Chem.* **1984,** *27*, 1575.
[2] R. M. Boden, M. Gates, S. Peng Ho, P. Sundararaman, *J. Org. Chem.* **1982,** *47*, 1347.
[3] H. Schmidhammer, F. Fritsch, W. P. Burkard, L. Eggstein-Aeppli, F. Hefti, M. I. Holck, *Helv. Chim. Acta* **1988,** *71*, 642.
[4] F. M. Hauser, T.-K. Chen, F. I. Carroll, *J. Med. Chem.* **1974,** *17*, 1117.
[5] I. Iijima, J. Minamikawa, A. E. Jacobson, A. Brossi, K. C. Rice, *J. Med. Chem.* **1978,** *21*, 398.
[6] J. D. Leander, P. D. Gesellchen, L. G. Mendelsohn, *Pharmacol. Biochem. Behav.* **1988,** *29*, 351.
[7] D. M. Zimmerman, J. D. Leander, J. K. Reel, M. D. Hynes, *J. Pharmacol. Exp. Ther.* **1987,** *241*, 374.
[8] L. L. Werling, G. D. Zaar, S. R. Brown, B. M. Cox, *J. Pharmacol. Exp. Ther.* **1985,** *233*, 722.