183. 5-Methylnaloxone and 5-Methylnaltrexone: Synthesis and Pharmacological Evaluation

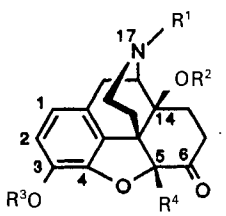
by **Helmut Schmidhammer***, **Karin Mayer-Valkanover**, and **Michaela Walla-Kugler**

Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a, A–6020 Innsbruck

(11.IX.90)

Starting from 5-methyl-oxycodone (**6**), 5-methylnaloxone (**4**), and 5-methylnaltrexone (**5**) have been prepared in several steps. Both **4** and **5** behaved as partial agonists in the AcOH writhing agonism and antagonism test in mice.

Introduction. – The opioid antagonist naloxone (**1**) is used to reverse the potentially lethal respiratory depression caused by neurolept analgesia and opioid overdose. Among other pharmacological effects, naloxone antagonizes the blood-pressure drop in various forms of shock [1] [2], reverses neonatal hypoxic apnea [3], counteracts chronic idiopathic constipation [4], and reduces the food intake in humans [5] [6]. Its *N*-cyclopropylmethyl congener naltrexone (**2**) was found to be orally active, to have greater potency and longer duration of action [7]. These properties made naltrexone suitable for the management of opioid dependence and provide an effective modality for the physician treating addict patients [8].



1 $R^1 = CH_2{=}CHCH_2$, $R^2 = R^3 = R^4 = H$
2 $R^1 = (CH_2)_2CHCH_2$, $R^2 = R^3 = R^4 = H$
3 $R^1 = R^2 = CH_3$, $R^3 = R^4 = H$
4 $R^1 = CH_2{=}CHCH_2$, $R^2 = R^3 = H$, $R^4 = CH_3$
5 $R^1 = (CH_2)_2CHCH_2$, $R^2 = R^3 = H$, $R^4 = CH_3$
6 $R^1 = R^3 = R^4 = CH_3$, $R^2 = H$
7 $R^1 = R^3 = R^4 = CH_3$, $R_2 = CH_3CO$
8 $R^1 = CH_3CH(Cl)OCO$, $R^2 = CH_3CO$, $R^3 = R^4 = CH_3$
9 $R^1 = CH_3CO$, $R^2 = H$, $R^3 = R^4 = CH_3$
10 $R^1 = H$, $R^2 = CH_3CO$, $R_3 = R_4 = CH_3$
11 $R^1 = R^2 = H$, $R^3 = R^4 = CH_3$
12 $R^1 = CH_2{=}CHCH_2$, $R^2 = H$, $R^3 = R^4 = CH_3$
13 $R^1 = (CH_2)_2CHCH_2$, $R^2 = H$, $R^3 = R^4 = CH_3$

In an effort to retain or improve the desirable pharmacological profile of naloxone and naltrexone, we directed our synthetic goals toward compounds having the basic structural features of these opioid antagonists. The introduction of a 5-Me group appeared reasonable since it was found that a 5-Me group could enhance the opioid properties of the already highly potent oxymorphone 14-*O*-methyl ether (**3**) [9] markedly [10]. Thus, we report on the synthesis and biological evaluation of 5-methylnaloxone (**4**) and 5-methylnaltrexone (**5**).

Chemistry. – Starting material for the synthesis of 5-methylnaloxone (**4**) and 5-methylnaltrexone (**5**) was 5-methyl-oxycodone (= 4,5α-epoxy-14-hydroxy-3-methoxy-5β,17-dimethylmorphinan-6-one; **6**) which is readily available from thebaine *via* 5-methylthebaine [11] [12] in three steps [13]. After protection of the 14-OH group by acetylation, **7** was *N*-demethylated using 1-chloroethyl chloroformate [14] in $CHCl_3$ in the presence of $NaHCO_3$. The resulting carbamate **8** was refluxed in MeOH to afford the rearranged amide **9** and not the secondary amine **10**. Similar O→N-acyl transfers in morphinans have been reported earlier [15] [16]. Attempts to hydrolyze **9** in 6N HCl or 10% KOH/EtOH failed, TLC showing a number of products. Finally, hydrolysis of **9** in 10% LiOH/EtOH was successfull (→**11**). Alkylation of **11** with either allyl bromide or cyclopropylmethyl chloride in DMF in the presence of K_2CO_3 yielded **12** and **13**, respectively. Ether cleavage was performed using 48% HBr solution to afford 5-methylnaloxone (**4**) and 5-methylnaltrexone (**5**).

Pharmacological Evaluation and Conclusion. – The 5-methylnaloxone (**4**) and 5-methylnaltrexone (**5**) were evaluated *in vitro* in opioid receptor binding studies (*Table 1*)[1]). [^{3}H]Naloxone (antagonist with preference for μ-opioid receptors) and [^{3}H]EKC

Table 1. *Opioid Receptor Binding Affinities*

Compound	[^{3}H]Naloxone (μ receptor) K_i [nM][a])	[^{3}H]EKC (κ receptor) K_i [nM][a])
4	20	51.3
5	10.6	18.1
Naloxone (**1**)	3.7	66.4
Naltrexone (**2**)	0.56	5.97

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

Table 2. *AcOH Writhing Agonism and Antagonism Test in Mice*

Compound	Antagonism Test		Agonism Test
	morphine [1.25 mg/kg] (μ) AD_{50}[a]) [mg/kg] (s.c.)	U-50,488H [2.5 mg/kg] (κ) AD_{50}[a]) [mg/kg] (s.c.)	ED_{50}[b]) [mg/kg] (s.c.)
4	1.02	–	7.1
5	0.48	–	5.1
Naloxone (**1**)	0.08	1.12	–
Naltrexone (**2**)	0.05	0.06	–
Morphine sulfate	–	–	0.39

[a]) The AD_{50} value (95% confidence limit) is defined as the dose at which the antinociceptive effect of the agonist was antagonized in 50% of the animals.

[b]) The ED_{50} value (95% confidence limit) is defined as the dose required for 50% reduction in frequency of writhing.

[1]) The tests were carried out for us at the *Lilly* Research Laboratories, *Eli Lilly and Company*, *Lilly* Corporate Center, Indianapolis, IN 46285, USA, through the courtesy of Dr. *D.D. Schoepp* (binding studies) and Dr. *J.D. Leander* (AcOH writhing tests).

(= [^{3}H]ethylketocyclazocine, κ-selective agonist) were used as ligands. Details of both procedures have been previously described [13] [17] (*Table 1*). *In vivo* studies included the AcOH writhing test for agonism [13] [18] [19] and the AcOH writhing antagonism test to assess antagonism [18] [19]. Morphine (μ-selective) and U-50,488H(κ-selective) were used as agonists (*Table 2*)[1]).

In the opioid receptor binding studies, **4** had *ca.* $^1/_6$ the affinity of naloxone (**1**) and **5** *ca.* $^1/_3$ the affinity of **1** for μ-receptor binding sites. In displacing [^{3}H]EKC (κ-selective) from its binding sites, **4** showed a similar potency as **1**, while **5** exhibited a 3–4 times higher potency than **1**.

In the AcOH writhing antagonism test, **5** showed *ca.* $^1/_6$ the potency of naloxone (**1**) and $^1/_{10}$ the potency of naltrexone (**2**) in antagonizing morphine-induced antinociception. Compound **4** was approximately half as potent. In counteracting U-50,488H-induced antinociception, both **4** and **5** were not active up to 2.5 mg/kg. In the AcOH writhing agonism test, both **4** and **5** exhibited weak agonist effects. These agonist effects are probably mediated through κ-receptors since **4** and **5** showed considerable κ-receptor binding, while the κ-selective agonist U-50,488H was not antagonized in the AcOH writhing antagonism test.

In conclusion, as 5-Me group in naloxone (**1**) and naltrexone (**2**) reduces the antagonist properties and enhances the agonist effects of these two opioid antagonists producing partial agonists.

Experimental Part

General. Column chromatography: alumina basic (70–230 mesh ASTM) from *Merck*. M.p.: *Kofler* melting point microscope, uncorrected. Optical rotations (concentration (g/100 ml), solvent): *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 rel. to Me_4Si as internal reference, *J* in Hz. Elemental analyses were performed at the Analytical Department of *F. Hoffmann-La Roche Ltd.*, Basel.

(−)-14β-Acetoxy-4,5α-epoxy-3-methoxy-5β,17-dimethylmorphinan-6-one (7). A soln. of **6** [13] (9.5 g, 28.84 mmol) in Ac_2O (40 ml) was refluxed for 20 min and then evaporated. The colorless, crystalline residue (10.72 g) was treated with boiling MeOH to give 10.44 g (97%) of **7** (m.p. 209–210°). An anal. sample was obtained by recrystallization from MeOH: m.p. 211–212°. $[\alpha]_D^{20} = -215.1$ (*c* = 1.19, $CHCl_3$). IR (KBr): 1710 (CO). ^{1}H-NMR ($CDCl_3$): 6.56 (*dd*, *J* = 8, 8, 2 arom. H); 4.12 (*m*, H–C(9)); 3.83 (*s*, CH_3O); 2.30 (*s*, CH_3N); 2.14 (*s*, CH_3CO); 1.61 (*s*, CH_3–C(5)). Anal. calc. for $C_{21}H_{25}NO_5 \cdot 0.2$ MeOH (377.84): C 67.39, H 6.88, N 3.71; found: C 67.25, H 6.95, N 3.75.

(−)-17-Acetyl-4,5α-epoxy-14β-hydroxy-3-methoxy-5β-methylmorphinan-6-one (**9**). A mixture of **7** (4.7 g, 12.7 mmol), $NaHCO_3$ (6.1 g, 76 mmol), 1-chloroethyl chloroformate (8.4 ml, 76 mmol), and 20 ml of EtOH-free $CHCl_3$ was stirred under reflux for 24 h. After filtration and evaporation of the filtrate, a nearly colorless oily residue (5.04 g of **8**) was obtained. This material was pure by TLC and used for further transformations without purification. After refluxing of **8** in MeOH (20 ml), the soln. was evaporated. The brownish oily residue was alkalinized with conc. NH_4OH soln. and extracted with $CHCl_3$ (2 × 20 ml) and the combined org. layer dried and evaporated. The brownish oily residue was crystallized with AcOEt: 3.3 g (73%) of **9** (m.p. 204–209°). A small portion of this material was recrystallized from AcOEt to give an anal. sample: m.p. 209–211°. $[\alpha]_D^{20} = -236.2$ (*c* = 0.90, $CHCl_3$). IR ($CHCl_3$): 3220 (OH), 1720 (CO), 1615 (amide). ^{1}H-NMR ($CDCl_3$): 6.60 (*dd*, *J* = 8, 8, 2 arom. H); 4.98 (*m*, H–C(9)); 3.87 (*s*, CH_3O); 2.12 (*s*, CH_3CO); 1.60 (*s*, CH_3–C(5)). Anal. calc. for $C_{20}H_{23}NO_5$ (357.41): C 67.21, H 6.49, N 3.92; found: C 67.59, H 6.42, N 4.03.

(−)-4,5α-Epoxy-14β-hydroxy-3-methoxy-5β-methlymorphinan-6-one Hydrobromide (= *N-Demethyl-5β-methyl-oxycodone Hydrobromide*: **11**·HBr). A soln. of LiOH·H_2O (1.2 g, 28.5 mmol) in H_2O (33 ml) was added to a soln. of **9** (3.4 g, 9.51 mmol) in EtOH (70 ml). This mixture was refluxed under N_2 for 46 h and then evaporated. The residue was partitioned between 30 ml of $CHCl_3$/MeOH 3:1 and 20 ml of H_2O, the org. layer washed with

brine, dried, and evaporated. The brown oily residue (2.86 g) was converted into the HBr salt **11**·HBr (1.38 g, 37%; m.p. 183–187° (MeOH)) in the usual way. A small portion of this material was recrystallized for analysis: m.p. 188–190° (MeOH). $[\alpha]_D^{20} = -109.3$ ($c = 0.97$, Me_2SO). IR (KBr): 3570, 3420, and 3280 (NH_2^+, OH), 1720 (CO). ^{1}H-NMR ((D_6) Me_2SO): 8.68 (br. *s*, NH_2^+); 6.66 (*dd*, $J = 8, 8, 2$ arom. H); 5.40 (*s*, OH); 3.77 (*s*, CH_3O); 1.46 (*s*, CH_3–C(5)). Anal. calc. for $C_{18}H_{21}NO_4 \cdot HBr \cdot 0.5$ MeOH (412.28): C 53.89, H 5.87, N 3.40, Br 19.38; found: C 54.25, H 6.11, N 3.46, Br 19.15.

(–)-17-Allyl-4,5α-epoxy-14β-hydroxy-3-methoxy-5β-methylmorphinan-6-one (= N-*Allyl*-N-*demethyl-5β-methyl-oxycodone*; **12**). A mixture of **11**·HBr (800 mg, 2.02 mmol), allyl bromide (0.19 ml, 2.22 mmol), K_2CO_3 (1.75 g, 12.7 mmol), and 8 ml of anh. DMF was stirred at 80° (bath temp.) for 30 min. The inorg. material was removed by filtration, the filtrate evaporated, and the oily residue (840 mg) dissolved in 15 ml of CH_2Cl_2. After washings with H_2O and brine, the org. layer was dried and evaporated to give 740 mg of a yellow oil which was crystallized with EtOH to afford 570 mg (79%; m.p. 135–139°) of **12** as colorless crystals. Recrystallization of a portion of this material gave an anal. sample: m.p. 137–140°. $[\alpha]_D^{24} = -175.4$ ($c = 0.70$, CH_2Cl_2). IR (KBr): 3360 (OH), 1720 (CO). ^{1}H-NMR ($CDCl_3$): 6.58 (*dd*, $J = 8, 8, 2$ arom H); 5.70 (*m*, 1 olef. H); 5.27 (*m*, 2 olef. H); 3.83 (*s*, CH_3O); 1.59 (*s*, CH_3–C(5)). Anal. calc. for $C_{21}H_{25}NO_4 \cdot 0.2$ EtOH (364.65): C 70.49, H 7.24, N 3.84; found: C 70.45, H 7.35, N 3.84.

(–)-17-(Cyclopropylmethyl)-4,5α-epoxy-14β-hydroxy-3-methoxy-5β-methylmorphinan-6-one Hydrobromide (= N-*(cylopropylmethyl)*-N-*demethyl-5β-methyl-oxycodone Hydrobromide*; **13**·HBr). A mixture of **11**·HBr (624 mg, 1.57 mmol), K_2CO_3 (1 g, 7.24 mmol), cyclopropylmethyl chlorid (0.175 ml, 1.88 mmol), and 20 ml of anh. DMF was stirred for 28 h at 100° (bath temp.). The inorg. material was filtered off, the filtrate evaporated, the residue dissolved in 15 ml of CH_2Cl_2, washed with H_2O and brine, dried, and evaporated. The residue (620 mg yellow oil) was chromatographed (alumina basic grade II, CH_2Cl_2) to give 515 mg of **13** as colorless oil which was converted in the usual way into the HBr salt: 452 mg (64%) of **13**·HBr. M.p. 265–274° (dec.; MeOH/Et_2O). $[\alpha]_D^{24} = -97.1$ ($c = 0.86$, Me_2SO). IR (KBr): 3240 (OH), 1720 (CO). ^{1}H-NMR ($CDCl_3$): 8.86, 5.85 (2*s*, OH, NH^+); 6.64 (*dd*, $J = 8, 8, 2$ arom. H); 3.90 (*s*, CH_3O), 1.58 (*s*, CH_3–C(5)). Anal. calc. for $C_{22}H_{28}NO_4 \cdot HBr \cdot 0.3$ MeOH (459.94): C 58.23, H 6.40, N 3.05; found: C 58.26, H 6.44, N 3.03.

(–)-17-Allyl-4,5α-epoxy-3,14β-dihydroxy-5β-methylmorphinan-6-on (= *5β-Methylnaloxone*; **4**). A soln. of **12** (400 mg, 1.13 mmol) in 5 ml of 48% HBr soln. was refluxed for 17 min and then evaporated. The residue was alkalinized with conc. NH_4OH soln., extracted with $CHCl_3$/MeOH 2:1 (2 × 10 ml), dried, and evaporated to give 310 mg of an oil which could not be crystallized. Conversion into the salicylate gave an oil which was treated with boiling (i-Pr)$_2O$ to yield 440 mg of **4**·salicylate as amorphous powder. A suspension in H_2O was alkalinized with conc. NH_4OH soln. and the precipitation isolated (235 mg) and recrystallized from MeOH: 158 mg (41%) of **4**. A portion was recrystallized from MeOH for analysis: m.p. 228–234° (dec.). $[\alpha]_D^{24} = -172.6$ ($c = 1.43$, CH_2Cl_2). IR (KBr): 3400 (OH), 1720 (CO). ^{1}H-NMR ($CDCl_3$): 6.64 (*d*, $J = 8$, 1 arom. H); 6.48 (*d*, $J = 8$, 1 arom. H); 5.65 (*m*, 1 olef. H); 5.24 (*m*, 1 olef. H); 1.58 (*s*, CH_3–C(5)). Anal. calc. for $C_{20}H_{23}NO_4 \cdot 0.25$ MeOH (349.42): C 69.61, H 6.92, N 4.01; found: C 69.66, H 7.01, N 4.00.

(–)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14β-dihydroxy-5β-methylmorphinan-6-one (= *5β-Methylnaltrexone*; **5**). A soln. of **13**·HBr (400 mg, 0.88 mmol) in 5 ml of 48% HBr soln. was refluxed for 17 min and then evaporated. The oily residue was suspensed in H_2O and alkalinized with conc. NH_4OH soln. and the resulting precipitation isolated and recrystallized from EtOH/H_2O: 227 mg (72%) of **5**. M.p. 135–138° $[\alpha]_D^{24} = -169.2$ ($c = 0.74$, CH_2Cl_2). IR (KBr): 3400 and 3240 (OH), 1720 (CO). ^{1}H-NMR ($CDCl_3$): 6.66 (*d*, $J = 8$, 1 arom. H); 6.48 (*d*, $J = 8$, 1 arom. H); 1.60 (*s*, CH_3–C(5)). Anal. calc. for $C_{21}H_{25}NO_4 \cdot 1.6\ H_2O$ (384.27): C 65.64, H 7.40, N 3.65; found: C 65.49, H 7.14, N 3.55.

Pharmacology. For opioid receptor binding tests, see [13] [17], and for AcOH writhing tests, see [13] [18] [19].

We are greatly indebted to Dr. *J. D. Leander* and Dr. *D. D. Schoepp, Eli Lilly and Company* for having provided us with the pharmacological data described herein. We are grateful to *Alkaloida, Chemical Works*, H-4440 Tiszavasvari, Hungary, for the generous gift of thebaine. We thank the Analytical Department of *F. Hoffmann-La Roche Ltd.*, Basel, for elemental analyses.

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