143. Synthesis and Biological Evaluation of 14-Alkoxymorphinans

Part 10[1])

14-*O*-Methyl Derivatives of 5-Methylnaltrexone and 5-Methylnaloxone

by **Helmut Schmidhammer**[2])* and **Christine Nussbaumer**

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

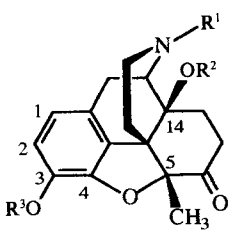
and **Dinesh Patel** and **John R. Traynor**

Department of Chemistry, Loughborough University of Technology, Loughborough, Leicestershire, LE11 3TU, U.K.

(11.V.94)

In several steps, 5,14-*O*-dimethylnaltrexone (**3**) and 5,14-*O*-dimethylnaloxone (**4**) were prepared starting from 5,14-*O*-dimethyloxycodone (**5**). Compound **3** exhibited opioid agonism *in vitro* (guinea-pig ileum and mouse *vas deferens* preparations) and antagonism *in vivo* (AcOH-writhing test in mice), while compound **4** was found to be an agonist *in vitro* and *in vivo*.

Introduction. – The 14-*O*-ethylation of 5-methylnaltrexone [2] (**1**) afforded compound **2**, which was found to be an opioid antagonist with unexpected *in vivo* activity. It does not antagonize morphine-induced antinociception in the AcOH-writhing test in mice, but it does block fentanyl- and sufentanil-induced antinociception in the same test. Such selectivity was not previously reported. Therefore, it was of interest to compare the pharmacology of 14-*O*-ethyl-5-methylnaltrexone (**2**) with the 14-OMe analogue **3**. Thus, we prepared 5,14-*O*-dimethylnaltrexone (**3**) and its *N*-allyl analogue **4**.



1 R^1 = cyclopropylmethyl, $R^2 = R^3$ = H
2 R^1 = cyclopropylmethyl, R^2 = Et, R^3 = H
3 R^1 = cyclopropylmethyl, R^2 = Me, R^3 = H
4 R^1 = allyl, R^2 = Me, R^3 = H
5 $R^1 = R^2 = R^3$ = Me
6 $R^1 = CO_2CHClCH_3$, $R^2 = R^3$ = Me
7 R^1 = H, $R^2 = R^3$ = Me
8 R^1 = cyclopropylmethyl, $R^2 = R^3$ = Me
9 R^1 = allyl, $R^2 = R^3$ = Me

Chemistry. – Starting material for the synthesis of compounds **3** and **4** was 5,14-*O*-dimethyloxycodone (= 4,5α-epoxy-3,14β-dimethoxy-5β,17-dimethylmorphinan-6-one; **5**) which is available from thebaine *via* 5-methylthebaine [3] [4] in four steps [5] [6].

[1]) Part 9: [1].

[2]) Present address: *Astra* Pain Research Unit, 275 bis, boulevard Armand Frappier, Edifice 3000, Laval, Quebec, Canada H7V 4A7.

N-Demethylation was carried out with 1-chloroethyl chloroformate [7] to give carbamate **6** as intermediate which was not further purified. Refluxing **6** in MeOH afforded *N*-demethylmorphinan **7**. Alkylation of **7** with either cyclopropylmethyl chloride or allyl bromide in DMF in the presence of K_2CO_3 yielded **8** and **9**, respectively. Ether cleavage with 48% HBr solution afforded 5,14-*O*-dimethylnaltrexone (**3**) and 4,14-*O*-dimethylnaloxone (**4**).

Pharmacological Evaluation. – Compounds **3** and **4** were evaluated *in vitro* by ligand binding (*Table 1*) in homogenates of guinea-pig brain using the selective ligands [^{3}H]DAMGO (μ), [^{3}H]DPDPE (δ), and [^{3}H]U69593 (κ), and by isolated-tissue bioassay using the guinea-pig myenteric plexus longitudinal muscle (GPI) and the mouse *vas deferens* preparations (MVD; *Table 2*). Naloxone, an antagonist with some preference for μ receptors, was used to define the receptor selectivity of the compounds.

Table 1. *Opioid Receptor Binding Studies*

	[^{3}H]DAMGO (μ) K_i [nM]	[^{3}H]U69593 (κ) K_i [nM]	[^{3}H]DPDPE (δ) K_i [nM]
3	2.06	1.99	12.4
4	3.81	16.6	9.58
2	1.2	1.1	4.1
Naloxone[a])	1.8	17.2	27.0

[a]) Values taken from [8].

Table 2. *Tissue Preparations* (GPI and MVD)

	GPI		MVD	
	IC_{50} [nM]	naloxone K_e[a]) [nM]	IC_{50}	naloxone K_e[a]) [nM]
3	35.2	0.47	21.5	1.83
4	2390	26.5	1490	32.4
2	> 10000		> 10000	

[a]) K_e = [antagonist]/DR-1, where DR is the dose ratio (*i.e.* ratio of equiactive concentrations of the test agonist in the presence of the antagonist).

Compounds **3** and **4** exhibited high (nM) affinity for the three opioid receptors μ, κ, and δ. Compound **3** showed approximately the same potency in displacing [^{3}H]DAMGO and [^{3}H]U69593 from their respective (μ and κ) binding sites, while it was somewhat less potent in displacing [^{3}H]DPDPE from δ-sites. Compound **4** exhibited a similar affinity for μ and δ binding sites, with reduced affinity for κ-sites.

In both, GPI and MVD preparations, compound **3** showed marked agonist activity. In contrast, **4** was *ca.* 70 times less potent as an agonist, and **2** showed no agonist properties when tested up to 10 μM. Antagonism of **3** by naloxone suggested the compound was acting as a μ-receptor agonist, while the higher K_e value determined against **4** suggested that the weak agonist activity of this compound was mediated by κ-receptors in the GPI and κ- and/or δ-receptors in the MVD.

For *in vivo* evaluation , the AcOH-writhing test was performed in mice[3]). Compound **3** showed no agonist activity but was able to antagonize the antinociceptive action of the μ-agonist morphine and the κ-agonist U50488H. In contrast, compound **4** exhibited agonism in this test (*Table 3*).

Table 3. *AcOH-Writhing Test in Mice*

	Agonism	Antagonism	
		morphine (μ; 1.25 mg/kg; *s.c.*) AD_{50}[a])[b])	U-50488H (κ; 2.5 mg/kg; *s.c.*) AD_{50}[a])[b])
3	n.e.[c])	0.56	2.3
4	i.w.[d])	n.e.[e])	n.e.[f])
Naloxone	–	0.08	1.12
2	n.e.[c])	n.e.[g])	n.e.[g])

[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]) AD_{50} values in mg/kg (*s.c.*)
[c]) No observable effect up to 5 mg/kg.
[d]) 39% inhibition of writhing was detected at 5 mg/kg.
[e]) No observable effect up to 1.25 mg/kg.
[f]) No observable effect up to 2.5 mg/kg.
[g]) No observable effect; no shift in the dose-effect curve of the agonist could be obtained.

Replacement of the 14-OEt group of **2** by a 14-OMe group to afford compound **3**, therefore, markedly changes the pharmacology. Thus, like **2**, **3** was an antagonist *in vivo*, but unlike **2** it did block morphine-induced antinociception. The fact that **3** also attenuated U50488H-induced antinociception agrees with the lack of selectivity of this group of compounds as shown by the binding assays. The *in vivo* findings are in contrast to the *in vitro* results which showed **3** and **4** to have agonist properties in both the GPI and the MVD. This is somewhat surprising since previous studies suggested the mouse writhing test to be the most sensitive test for μ- and κ-opioid agonists [9]. In conclusion, 14-OMe analogues **3** and **4** do not retain the unique pharmacological properties of **2**.

Experimental Part

General. M.p.: *Kofler* melting-point microscope; uncorrected. Optical rotations: *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 rel. to $SiMe_4$ as internal reference, *J* in Hz. Elemental analyses were performed at the Analytical Department of *F. Hoffmann-La Roche AG*, Basel.

(−)-3,14β-Dimethoxy-4,5α-epoxy-5β-methylmorphinan-6-one Hydrochloride (**7**·HCl). A mixture of **5** (7.0 g, 20.38 mmol), $KHCO_3$ (10.2 g, 101.9 mmol), 1-chloroethyl chloroformate (13.4 ml, 122.3 mmol), and CH_2Cl_2 (100 ml) was stirred under reflux for 5 h. The inorg. material was filtered off and the filtrate evaporated to yield 9.81 g of **6** as a slightly yellow oil (pure by TLC) which was not further purified and characterized. After refluxing a soln. of this oil in MeOH (50 ml) for 30 min, the soln. was evaporated. The resulting colorless foam (8.42 g) was crystallized from MeOH/Et_2O: 7.82 g (91%) of **7**·HCl. A small portion of this material was recrystallized from

[3]) This test was carried out for us at the *Lilly* Research Laboratories, *Eli Lilly & Co.*, *Lilly* Corporate Center, Indianapolis, Indiana 46285, USA, through the courtesy of Dr. *J. D. Leander*.

MeOH/Et_2O for analysis. M.p. 199–204° (dec.). $[\alpha]_D^{20} = -130.1$ ($c = 1.23$, $CHCl_3$). IR (KBr): 3400 (NH_2^+), 1720 (CO). ^{1}H-NMR ((D$_6$)DMSO): 9.98, 8.40 (2 br. *s*, NH_2^+); 6.64 (*dd*, $J = 8, 8, 2$ arom. H); 3.73 (*s*, MeO–C(3)); 3.32 (*s*, MeO–C(14)); 1.48 (*s*, Me–C(5)). Anal. calc. for $C_{19}H_{23}NO_4 \cdot HCl \cdot 0.5\ H_2O \cdot 0.5$ MeOH (390.88): C 59.91, H 6.96, Cl 9.07, N 3.58; found: C 59.52, H 7.02, Cl 9.29, N 3.50.

(–)-17-(Cyclopropylmethyl)-4,5α-epoxy-3,14β-dimethoxy-5β-methylmorphinan-6-one (**8**). A mixture of **7**·HCl (2.0 g, 5.12 mmol), K_2CO_3 (3.1 g, 22.43 mmol), cyclopropylmethyl chloride (0.6 ml, 6.14 mmol), and anh. DMF (20 ml) was stirred for 22 h at 100° (bath temp.). The inorg. material was filtered off, the filtrate evaporated, the oily residue partitioned between CH_2Cl_2 and H_2O, and the org. layer washed with brine, dried, and evaporated: 2.0 g of brown oil. This oil was chromatographed (basic alumina, grade II, CH_2Cl_2): 1.81 g (86%) of **8** as a colorless oil. A small portion was converted into **8**·HBr for analysis. M.p. 258–261° (dec.; acetone). $[\alpha]_D^{20} = -149.5$ ($c = 0.93$, $CHCl_3$). IR (KBr): 3600, 3400 (NH^+, OH), 1720 (CO). ^{1}H-NMR ($CDCl_3$): 9.32 (br. *s*, NH^+); 6.66 (*s*, 2 arom. H); 3.94 (*s*, MeO–C(3)); 3.56 (*s*, MeO–C(14)); 1.63 (*s*, Me–C(5)). Anal. calc. for $C_{23}H_{29}NO_4 \cdot HBr \cdot 0.5\ H_2O$ (473.41): C 58.35, H 6.60, Br 16.88, N 2.96; found: C 58.45, H 6.63, Br 16.82, N 2.94.

(–)-17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-14β-methoxy-5β-methylmorphinan-6-one (**3**). A soln. of **8** (950 mg, 2.42 mmol) in 48% HBr soln. (10 ml) was refluxed for 15 min. After addition of ice, the soln. was alkalinized with conc. NH_4OH soln. and extracted with $CHCl_3$/MeOH 3:2 (3 × 20 ml), the combined org. layer dried and evaporated and the resulting slightly pink foam (802 mg) crystallized from MeOH: 505 mg (62%) of **3**. An anal. sample was prepared by recrystallization of a small portion from MeOH. M.p. 177–179°. $[\alpha]_D^{20} = -153.0$ ($c = 0.93$, $CHCl_3$). IR (KBr): 3500 (OH), 1720 (CO). ^{1}H-NMR ((D$_6$)DMSO): 8.73 (br. *s*, OH); 6.30 (*s*, 2 arom. H); 3.56 (*s*, MeO); 1.43 (*s*, Me–C(5)). Anal. calc. for $C_{22}H_{27}NO_4 \cdot 0.9$ MeOH (398.30): C 69.06, H 7.74, N 3.52; found: C 69.24, H 7.97, N 3.47.

(–)-17-Allyl-4,5α-epoxy-3,14β-dimethoxy-5β-methylmorphinan-6-one (**9**). A mixture of **7**·HCl (2.25 g, 5.76 mmol), allyl bromide (0.56 ml, 6.33 mmol), K_2CO_3 (2.0 g, 14.5 mmol) and anh. DMF (10 ml) was stirred at 80° (bath temp.) for 30 min. After filtration, the filtrate was evaporated, the oily residue partitioned between CH_2Cl_2 and H_2O, the org. layer washed with brine, dried, and evaporated, and the resulting residue (2.1 g yellowish oil) crystallized with EtOH: 1.36 g of **9** as colorless crystals. From the mother liquor another 240 mg of **9** with similar quality were obtained. Total yield 1.6 g (75%). M.p. 90–92°. $[\alpha]_D^{20} = -201.1$ ($c = 0.92$, $CHCl_3$). IR (KBr): 1720 (CO). ^{1}H-NMR ($CDCl_3$): 6.69 (*dd*, $J = 8, 8, 2$ arom. H); 5.86 (*m*, 1 olef. H); 5.30 (*m*, 2 olef. H); 3.88 (*s*, MeO–C(3)); 3.30 (*s*, MeO–C(14)); 1.61 (*s*, Me–C(5)). Anal. calc. for $C_{22}H_{27}NO_4$ (369.45): C 71.52, H 7.37, N 3.79; found: C 71.13, H 7.53, N 3.75.

(–)-17-Allyl-4,5α-epoxy-3-hydroxy-14β-methoxy-5β-methylmorphinan-6-one (**4**). A soln. of 9 (1.2 g, 3.25 mmol) in 48% HBr soln. (7 ml) was refluxed for 15 min. After addition of ice, the soln. was alkalinized with conc. NH_4OH soln., extracted with $CHCl_3$/MeOH: 3:2 (3 × 20 ml), the combined org. layer dried and evaporated, and the resulting residue (1.13 g of slightly brown foam) crystallized from MeOH: 1.03 g (90%) of **4**. An anal. sample was obtained by recrystallization of a small amount. M.p. 163–166°. $[\alpha]_D^{20} = -174.0$ ($c = 0.85$, $CHCl_3$). IR (KBr): 3400, 3220 (OH), 1720 (CO). ^{1}H-NMR ((D$_6$)DMSO): 8.90 (br. *s*, OH); 6.40 (*s*, 2 arom. H); 5.71 (*m*, 1 olef. H); 5.16 (*m*, 2 olef. H); 3.17 (*s*, MeO); 1.41 (*s*, Me–C(5)). Anal. calc. for $C_{21}H_{25}NO_4 \cdot 1.5$ MeOH $\cdot 0.5\ H_2O$ (412.50): C 65.51, H 7.82, N 3.40; found: C 65.67, H 7.77, N 3.39.

Pharmacology. Opioid receptor binding was performed in homogenates of guinea-pig brain in *Tris*·HCl buffer (50 mM, pH 7.4) for 40 min at 25°, as previously described [10]. For GPI and MVD, see [10] [11]. For the AcOH-writhing test, see [6] [12] [13].

We are greatly indebted to Dr. *J. D. Leander, Eli Lilly & Co.* for having provided us with the pharmacological data of the AcOH-writhing test. We wish to thank the Analytical Department of *F. Hoffmann-La Roche AG*, Basel, for elemental analyses.

REFERENCES

[1] H. Schmidhammer, A. Schratz, C. Schmidt, D. Patel, J. R. Traynor, *Helv. Chim. Acta* **1993,** *76,* 476.
[2] H. Schmidhammer, K. Mayer-Valkanover, M. Walla-Kugler, *Helv. Chim. Acta* **1990,** *73,* 1986.
[3] R. M. Boden, M. Gates, S. Ho Peng, P. Sundararaman, *J. Org. Chem.* **1982,** *47,* 1347.
[4] H. Schmidhammer, F. Fritsch, W. P. Burkard, L. Eggstein-Aeppli, M. I. Holck, *Helv. Chim. Acta* **1988,** *71,* 642.
[5] H. Schmidhammer, A. Schratz, J. Mitterdorfer, *Helv. Chim. Acta* **1990,** *73,* 1784.
[6] H. Schmidhammer, J. B. Deeter, N. D. Jones, J. D. Leander, D. D. Schoepp, J. K. Swartzendruber, *Helv. Chim. Acta* **1988,** *71,* 1801.
[7] R. A. Olofson, J. T. Marts, J.-P. Senet, M. Piteau, T. Malfroot, *J. Org. Chem.* **1984,** *49,* 2081.
[8] I. Magnan, S. I. Paterson, A. Tavani, H. W. Kosterlitz, *N. S. Arch. Pharmacol.* **1982,** *319,* 197.
[9] A. G. Hayes, M. J. Sheehan, M. B. Tyers, *Br. J. Pharmacol.* **1987,** *91,* 823a.
[10] F. D. Rodriguez, E. Bardall, J. R. Traynor, *J. Neurochem.* **1992,** *59,* 467.
[11] T. G. Franklin, J. R. Traynor, *Mol. Neuropharmacol.* **1992,** *1,* 187.
[12] D. M. Zimmerman, J. D. Leander, J. K. Reel, M. D. Hynes, *J. Pharmacol. Exp. Ther.* **1987,** *241,* 374.
[13] J. D. Leander, P. D. Gesellchen, L. G. Mendelsohn, *Pharmacol. Biochem. Behav.* **1988,** *29,* 351.