160. Synthesis and Biological Evaluation of 14-Alkoxymorphinans

Part 7[1])

14,14'-Dimethoxy Analogues of Norbinaltorphimine: Synthesis and Determination of Their $\varkappa$ Opioid Antagonist Selectivity

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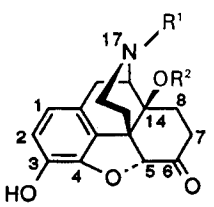
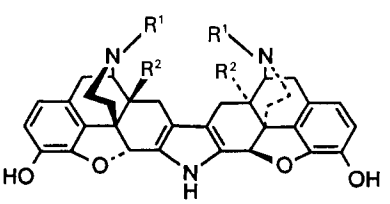
(5.VII.90)

The bimorphinans **6** and **7** have been prepared from 14-*O*-methylnaloxone (**2**) and 14-*O*-methylnaltrexone (**3**), respectively. The known compounds **2** and **3** were sythesized by a different route than the route described. Bimorphinan **7** possessed a similar $\varkappa$ receptor affinity to norbinaltorphimine (**1**) but had a reduced selectivity due to marked increases in μ- and δ-receptor affinity. Bimorphinan **6** was both a less selective and less potent $\varkappa$ antagonist than **1**.

Introduction. – The existence of three major types of opioid receptors (μ, $\varkappa$, and δ) is generally recognized [2]. Endogenous ligands for the opioid receptors have been identified and their individual pharmacological activities explored [3–5]. In addition to the modulation of pain experience, opioid receptors and their endogenous peptide ligands are known to have important physiological functions [6] [7]. The fact that sub-populations of opioid receptors are frequently associated with different physiological effects has created a need for highly selective opioid antagonists which can be used as pharmacological and biological tools. Since it is desireable that ligands are stable against peptidases and are capable of entering the central nervous system easily, non-peptide antagonists have been



2 $R^1 = CH_2{=}CH{-}CH_2$, $R^2 = CH_3$
3 R^1 = Cyclopropylmethyl, $R^2 = CH_3$
4 $R^1 = CH_2{=}CH{-}CH_2$, R^2 = H (naloxone)
5 R^1 = Cyclopropylmethyl, R^2 = H (naltrexone)



1 R^1 = Cyclopropylmethyl, R^2 = OH
6 $R^1 = CH_2{=}CH{-}CH_2$
7 R^1 = Cyclopropylmethyl, $R^2 = OCH_3$

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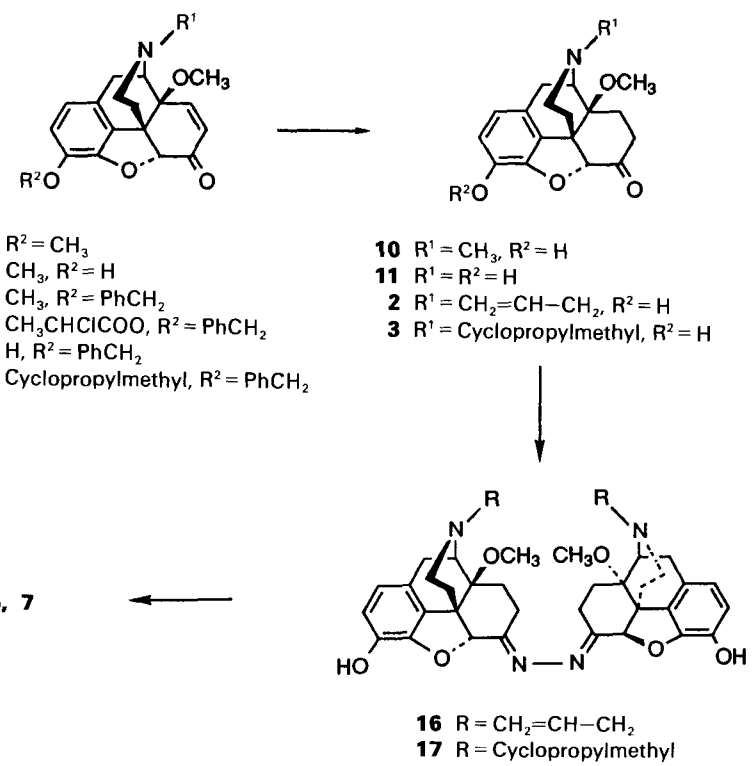
developed for this purpose. Highly selective non-peptide, competitive antagonists have been reported for μ (cyprodime [8] [9]), $\varkappa$ (norbinaltorphimine, **1** [10] [11]), and δ receptors (naltrindole [12]).

14-*O*-Methylnaloxone (**2**) and 14-*O*-methylnaltrexone (**3**) were found to possess similar pharmacological properties to the opioid antagonists naloxone (**4**) and naltrexone (**5**), respectively [13]. It was of interest to prepare, from **2** and **3**, bimorphinans linked by a pyrrole spacer (compounds **6** and **7**, respectively) and to determine the $\varkappa$-opioid-antagonist selectivity of these compounds in comparison to norbinaltorphimine (**1**), the corresponding bimorphinan of naltrexone.

Chemistry. – Since the preparation of 14-*O*-methylnaloxone (**2**) and 14-*O*-methylnaltrexone (**3**) by the method of *Kobylecki et al.* [13] gave, in our hands, unsatisfactory results in the last step of the reaction sequence (3-OCH_3 ether cleavage with BBr_3), we sought for an alternative route for the synthesis of **2** and **3**. Our strategy was to perform the 3-OCH_3 ether cleavage at an earlier step of the synthesis. Thus, 3-OCH_3 ether cleavage of 14-methoxycodeinone (**8**) [13] with 48% HBr solution gave 14-methoxymorphinone (**9**) in good yield (*Scheme*). Catalytic hydrogenation of **9** over Pd/C afforded 14-*O*-methyloxymorphone (**10**) [14]. Next step, *N*-demethylation of **10** with 1-chloroethyl chloroformate, has been already described [15]. *N*-Normorphinan **11** was alkylated with allyl bromide in acetone at room temperature to afford 14-*O*-methylnaloxone (**2**).

Scheme



For the synthesis of 14-*O*-methylnaltrexone (**3**), 14-methoxymorphinone (**9**) was first 3-*O*-benzylated, then the *N*-Me group of **12** was removed with 1-chloroethyl chloroformate. Carbamate **13**, which was not further purified and characterized, was refluxed in MeOH to yield *N*-demethyl derivative **14**. Alkylation with cyclopropylmethyl chloride gave morphinone **15**, which was hydrogenated over Pd/C to afford 14-*O*-methylnaltrexone (**3**).

Bimorphinans **6** and **7** were prepared *via* the azines **16** and **17**, respectively. Thus, treatment of compounds **2** and **3** with hydrazine hydrate in MeOH gave the azines **16** and **17**, respectively. The desired pyrroles **6** and **7** were obtained by heating **16** and **17** with CH_3SO_3H in DMSO.

Pharmacology. – Compounds **6** and **7** were evaluated *in vitro* for opioid-agonist and -antagonist properties in the isolated guinea-pig ileal longitudinal muscle preparation (GPI) and the mouse vas deferens preparation (MVD) [8] [9]. Antagonist potencies at the three opioid receptors were determined against normorphine (μ-selective agonist), ethylketocyclazocine (κ-selective agonist), and [D-Ala^2, D-Leu^5]enkephalin (a mixed μ/δ agonist which is very δ-selective in the MVD due to the high δ-receptor reserve in this preparation, *cf.* the *Table*).

Table. *Opioid Antagonist Activity of* **6**, **7**, *and Norbinaltorphimine* (**1**) *in the GPI and MVD*

Antagonist	*Ke*[a]) [nM]			Selectivity ratio	
	Ethylketocyclazocine (κ)[b])	Normorphine (μ)[b])	[D-Ala^2, D-Leu^5] enkephalin (δ)[c])	μ/κ	δ/κ
6	0.6	88	4.6	147	8
7	0.03	0.36	2.3	12	77
1	0.02	27	22	1350	1100

[a]) *Ke* = [antagonist]/DR-1, where DR is the dose ratio (*i.e.* ratio of equiactive concentrations of the test agonist in the presence and absence of the antagonist). [b]) Determined in the GPI. [c]) Determined in the MVD.

Bimorphinans **6** and **7** did not show any agonist activity in GPI and MVD. They exhibited opioid antagonist potency and preference for κ receptors. The affinity of compound **7** for κ receptors was similar to the affinity of norbinaltorphimine (**1**), while the κ-selectivity of **7** was lower due to an increase in μ- and δ-receptor affinity. Compound **6** exhibited *ca.* one-twentieth of the κ-receptor affinity of **7** and possessed also a lower κ selectivity.

We are indebted to *Alkaloida, Chemical Factory*, H–4440 Tiszavasvari, for the generous gift of thebaine. We thank Prof. Dr. *K.-H. Ongania* for performing the mass spectra and Mag. *H.-P. Kählig* for recording the 300-MHz ^{1}H-NMR spectra (both at the Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck). We further thank Dr. *J. Zak*, Institute of Physical Chemistry, University of Vienna, for elemental analyses.

Experimental Part

General. M.p.: *Kofler* melting-point microscope; uncorrected. Prep. TLC: silica-gel plates (Kieselgel *60 F*; 2 mm) from *Merck*; $CHCl_3$/MeOH/NH_4OH 85:14:1. Column chromatography: basic alumina (70–230 mesh ASTM) from *Merck*. $[\alpha]_D$: *c* in g/100 ml, *Perkin Elmer 141* polarimeter. IR spectra (in cm^{-1}): *Beckman Acculab 2* apparatus. ^{1}H-NMR spectra: *Bruker AM 300* spectrometer or *Jeol-JNM-PMX-60* spectrometer; δ in ppm relative to TMS as internal reference, *J* (apparent coupling constant) in Hz. CI-MS: *Finnigan MAT 44S* apparatus and *VG-7035* mass spectrometer.

7,8-Didehydro-4,5α-epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6-one Hydrobromide (= *14β-Methoxymorphinone Hydrobromide*; **9**·HBr). A soln. of **8** [13] (5.0 g, 15.3 mmol) in 20 ml of 48% HBr soln. was refluxed for 17 min and then evaporated. The oily residue was crystallized from MeOH to yield 4.5 g (75%) of **9**·HBr as gray-green crystals. An anal. sample was obtained by recrystallization of a small amount from MeOH. M.p. > 260° (dec.). $[\alpha]_D^{22} = -66.7$ ($c = 0.91$, DMF). IR (KBr): 3430, 3140 (OH, $^+$NH); 1675 (CO). ^{1}H-NMR ((D$_6$) DMSO; 60 MHz): 9.45 (*s*, OH, $^+$NH); 6.82 (*d*, $J = 10$, 1 olef. H); 6.63 (*s*, 2 arom. H); 6.32 (*d*, $J = 10$, 1 olef. H), 5.07 (*s*, H–C(5)); 3.22 (*s*, CH_3O); 2.90 (*s*, CH_3N^+). Anal. calc. for $C_{18}H_{19}NO_4 \cdot HBr \cdot 0.5$ MeOH (410.29): C 54.16, H 5.41, N 3.41, Br 19.48; found: C 53.78, H 5.54, N 3.28, Br 19.33.

4,5α-Epoxy-3-hydroxy-14β-methoxy-17-methylmorphinan-6-one Hydrobromide (= *14-O-Methyloxymorphone Hydrobromide*; **10**·HBr) [14]. A mixture of **9**·HBr (2.4 g, 6.1 mmol), 240 mg of 10% Pd/C-catalyst, and 150 ml of MeOH was hydrogenated at r.t. and 30 psi for 2 h. The catalyst was filtered off, the filtrate evaporated, and the colorless crystalline residue treated with little MeOH to yield 2.0 g (83%) of **10**·HBr. M.p. > 300° (dec.) ([14]: > 300° (dec.; MeOH)). This material was identical by TLC, IR, and ^{1}H-NMR with authentic material [14].

4,5α-Epoxy-3-hydroxy-14β-methoxy-17-(prop-2-enyl)morphinan-6-one (= *14-O-Methylnaloxone*; **2**) [13]. A mixture of **11**·HCl [15] (1.48 g, 4.4 mmol), allyl bromide (0.41 ml, 4.8 mmol), $NaHCO_3$ (800 mg, 9.6 mmol), and 50 ml of anh. acetone was stirred at r.t. for 1 week. After filtration, the filtrate was evaporated and the yellowish, oily residue crystallized with MeOH to give 2.56 g (43%) of **2** as colorless crystals. M.p. 195–198° ([13]: 197–199° (Et_2O/petroleum ether)).

3-(Benzyloxy)-7,8-didehydro-4,5α-epoxy-14β-methoxy-17-methylmorphinan-6-one (**12**). A mixture of **9**·HBr (10.4 g, 25.35 mmol), $PhCH_2Br$ (3.54 ml, 29.8 mmol), K_2CO_3 (10.4 g, 75.2 mmol), and 50 ml of anh. DMF was stirred under N_2 at r.t. for 20 h. After addition of 400 ml of H_2O, the mixture was extracted with AcOEt (3 × 100 ml). The combined org. layers were washed with H_2O (2 × 200 ml) and brine, and then evaporated. The residue (8.25 g brown oil) was crystallized with MeOH to yield 6.4 g (60%) of **12**. M.p. 180–183°. A small portion was recrystallized from MeOH for analysis. M.p. 182–184°. $[\alpha]_D^{20} = -35.6$ ($c = 0.9$, $CHCl_3$). IR (KBr): 1675 (CO). ^{1}H-NMR ($CDCl_3$; 300 MHz): 7.34 (*m*, 5 arom. H); 6.71 (*d*, $J = 8$, 1 arom. H); 6.61 (*d*, $J = 10$, 1 olef. H); 6.55 (*d*, $J = 8$, 1 arom. H); 6.26 (*d*, $J = 10$, 1 olef. H); 5.16 (*s*, CH_2O); 4.77 (*s*, H–C(5)); 3.28 (*s*, CH_3O); 2.48 (*s*, CH_3N). CI-MS: 404 ($[M + 1]^+$). Anal. calc. for $C_{25}H_{25}NO_4$ (403.48): C 74.42, H 6.25, N 3.47; found: C 74.40, H 6.37, N 3.58.

3-(Benzyloxy)-7,8-didehydro-4,5α-expoxy-14β-methoxymorphinan-6-one (**14**). A mixture of **12** (3.8 g, 9.44 mmol), $NaHCO_3$ (6.4 g, 76.3 mmol), 1-chloroethyl chloroformate (8.3 ml, 76.3 mmol), and $ClCH_2CH_2Cl$ (15 ml) was stirred for 20 h at 60–65° (bath temp.). After filtration, the filtrate was evaporated to give 4.07 g of **13** as a slightly brown oil which was not further purified and characterized but refluxed in MeOH (15 ml) for 1 h. Then, the soln. was evaporated to give 3.87 g of a slightly brown foam which was alkalized with conc. NH_4OH soln. and extracted with CH_2Cl_2 (2 × 40 ml, 1 × 20 ml). The combined org. layers were washed with H_2O (3 × 20 ml) and brine, dried, and evaporated to give 3.43 g of a brownish oil. This oil was chromatographed on alumina basic grade IV (length of the column 30 cm, diameter 3.5 cm, elution with CH_2Cl_2) to yield 2.9 g of colorless oil which was crystallized from MeOH to give 2.71 g (74%) of **12**. An anal. sample was obtained by recrystallization of a small sample from MeOH. M.p. 80–82°. $[\alpha]_D^{20} = -13.4$ ($c = 1.06$, $CHCl_3$). IR (KBr): 3300 (NH), 1675 (CO). ^{1}H-NMR ($CDCl_3$; 60 MHz): 7.32 (*m*, 5 arom. H); 6.72 (*d*, $J = 10$, 1 olef. H); 6.64 (*d*, $J = 8$, 1 arom. H); 6.46 (*d*, $J = 8$, 1 arom. H); 6.27 (*d*, $J = 10$, 1 olef. H); 5.08 (*s*, CH_2O); 4.63 (*s*, H–C(5)); 3.20 (*s*, CH_3O). CI-MS: 390 ($[M + 1]^+$). Anal. calc. for $C_{24}H_{23}NO_4 \cdot 0.3$ MeOH (299.04): C 73.14, H 6.11, N 3.51; found: C 73.03, H 6.07, N 3.83.

3-(Benzyloxy)-17-(cyclopropylmethyl)-7,8-didehydro-4,5α-expoxy-14β-methoxymorphinan-6-one (**15**). A mixture of **14** (2.17 g, 5.6 mmol), K_2CO_3 (2.2 g, 15.9 mmol), cyclopropylmethyl chloride (0.61 ml, 6.6 mmol), and anh. DMF (10 ml) was stirred at 90° (bath temp.) for 20 h. After addition of H_2O (200 ml), the mixture was extracted with Et_2O (3 × 30 ml), the combined org. layers were washed with H_2O (3 × 80 ml) and brine, dried, and evaporated to give 2.5 g of a brown oil. This oil was chromatographed on alumina basic grade II (length of the column 25 cm, diameter 3.5 cm, elution with CH_2Cl_2) to give 1.9 g of a colorless oil which was crystallized from MeOH to yield 1.78 g (72%) of **15**. A small portion of this material was recrystallized from MeOH for analysis. M.p. 102–104°. $[\alpha]_D^{20} = -85.9$ ($c = 1.03$, $CHCl_3$). IR (KBr): 1675 (CO). ^{1}H-NMR ($CDCl_3$; 300 MHz): 7.35 (*m*, 5 arom. H); 6.73 (*d*, $J = 8$, 1 arom. H); 6.69 (*d*, $J = 10$, 1 olef. H); 6.52 (*d*, $J = 8$, 1 arom. H); 6.22 (*d*, $J = 10$, 1 olef. H); 5.15 (*s*, CH_2O); 4.74 (*s*, H–C(5)); 3.33 (*s*, CH_3O). CI-MS: 444 ($[M + 1]^+$). Anal. calc. for $C_{28}H_{29}NO_4 \cdot 0.3$ MeOH (453.15): C 75.00, H 6.72, N 3.09; found: C 74.84, H 6.56, N 3.19.

17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-14β-methoxymorphinan-6-one (= *14-O-Methylnaltrexone*; **3**) [13]. A mixture of **15** (1.5 g, 3.4 mmol), 10% Pd/C-catalyst (200 mg), and MeOH (50 ml) was hydrogenated at r.t. and 40–50 psi for 5 h. The catalyst was filtered off and the filtrate evaporated. The residue (1.26 g slightly brown oil) was crystallized from $(i\text{-}Pr)_2O$ to yield 1.07 g (89%) of **3**. M.p. 184–187° ([13]: 187–188° (petroleum ether)).

14-O-Methylnaloxone Azine (**16**). A soln. of **2** (500 mg, 1.5 mmol) and hydrazine hydrate (375 mg, 0.75 mmol) in MeOH (3 ml) was refluxed for 24 h (the product (**16**) began to crystallize after *ca.* 3 h). After cooling for 16 h at + 4°, 306 mg (61%) of **16** were isolated. M.p. > 190° (dec.). IR (KBr): 3200 (OH), 1635 (C=N). ^{1}H-NMR ($CDCl_3$; 300 MHz): 6.68 (*d*, *J* = 8, 1 arom. H); 6.52 (*d*, *J* = 8, 1 arom. H); 5.87 (*m*, 1 olef. H); 5.18 (*m*, 2 olef. H); 4.93 (*s*, H–C(5)); 3.21 (*s*, CH_3O). Anal. calc. for $C_{40}H_{46}N_4O_6 \cdot H_2O$ (714.83): C 67.20, H 7.05, N 7.84; found: C 67.12, H 6.83, N 7.78.

14-O-Methylnaltrexone Azine (**17**). A soln. of **3** (560 mg, 1.6 mmol) and hydrazine hydrate (39.5 mg, 0.8 mmol) in MeOH (3 ml) was refluxed for 21 h. After addition of H_2O (6 ml) and extractions with CH_2Cl_2 (3 × 5 ml), the org. layers were combined, washed with H_2O (3 × 10 ml), and evaporated. The residue (545 mg brownish oil) was crystallized from MeOH to afford 472 mg (82%) of **17**. An anal. sample was obtained by recrystallization of a small portion of this material from MeOH. M.p. > 195° (dec.). IR (KBr): 3350 (OH), 1630 (C=N). ^{1}H-NMR ($CDCl_3$; 300 MHz): 6.63 (*d*, *J* = 8, 1 arom. H); 6.49 (*d*, *J* = 8, 1 arom. H); 4.93 (*s*, H–C(5)); 3.28 (*s*, CH_3O). Anal. calc. for $C_{42}H_{50}N_4O_6 \cdot 1.5\ H_2O$ (733.87): C 68.73, H 7.28, N 7.63; found: C 68.37, H 7.16, N 7.70.

6,6',7,7'-Tetradehydro-4,5α:4',5'α-diepoxy-14β,14'β-dimethoxy-17,17'-di(prop-2-enyl)-6,6'-(epimino)[7,7'-bimorphinan]-3,3'-diol (**6**). A soln. of **2** (300 mg, 0.42 mmol) and MsOH (170 mg, 1.8 mmol) in anh. DMSO (3 ml) was stirred under N_2 at 130° (bath temp.) for 1 h. The cooled soln. was alkalized with conc. NH_4OH soln. extracted with CH_2Cl_2 (3 × 10 ml), the combined org. layers were washed with H_2O (2 × 15 ml), dried, and evaporated. The residue (287 mg brown oil) was purified by prep. TLC (2 plates were used) to give 79 mg (27%) of **6** as slightly yellow powder. M.p. > 220° (dec.). IR (KBr): 3280 (OH). ^{1}H-NMR (CD_3OD; 300 MHz): 6.65 (*d*, *J* = 8, 2 arom. H); 6.59 (*d*, *J* = 8, 2 arom. H); 5.96 (*m*, 2 olef. H); 5.48 (*s*, H–C(5), H–C(5')); 5.33 (*m*, 4 olef. H); 3.12 (*s*, CH_3O–C(14), CH_3O–C(14')). CI-MS: 662 ([*M* + 1]$^+$). Anal. calc. for $C_{40}H_{43}N_3O_6 \cdot 2\ H_2O$ (697.80): C 68.84, H 6.79, N 6.02; found: C 68.58, H 6.57, N 5.99.

17,17'-Bis(cyclopropylmethyl)-6,6',7,7'-tetradehydro-4,5α:4',5'α-diepoxy-14β,14'β-dimethoxy-6,6'-(epimino)-[7,7'-bimorphinan]-3,3'-diol (**7**). A soln. of **3** (332 mg, 0.45 mmol) and MsOH (450 mg, 4.7 mmol) in anh. DMSO (2 ml) was stirred under N_2 at 130° (bath temp.) for 1 h. The cooled soln. was alkalized with conc. NH_4OH soln., extracted with CH_2Cl_2 (3 × 10 ml), the combined org. layers were washed with H_2O (3 × 10 ml) dried, and evaporated. The residue (298 mg brown oil) was purified by prep. TLC (2 plates were used) to yield 74 mg (24%) of **7** as slightly brown powder. M.p. > 200° (dec.). IR (KBr): 3400 (OH). ^{1}H-NMR ($CDCl_3$; 300 MHz): 6.68 (*d*, *J* = 8, 2 arom. H); 6.48 (*d*, *J* = 8, 2 arom. H); 5.61 (*s*, H–C(5), H–C(5')); 3.18 (*s*, CH_3O–C(14), CH_3O–C(14')). CI-MS: 690 ([*M* + 1]$^+$). Anal. calc. for $C_{42}H_3N_3O_6 \cdot 1.5\ H_2O$ (716.84): C 70.37, H 6.98, N 5.94; found: C 70.23, H 7.16, N 5.98.

Pharmacology. See [8] [9].

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