SYNTHESIS AND BIOLOGICAL EVALUATION OF 14-ALKOXYMORPHINANS. 16.[1] 14-*O*-ALKYL DERIVATIVES OF THE μ OPIOID RECEPTOR ANTAGONIST CYPRODIME[#]

Helmut Schmidhammer,*[a] Roland Krassnig,[a] Elisabeth Greiner,[a] and John R. Traynor*[b,Δ]

a: Institute of Pharmaceutical Chemistry, University of Innsbruck, Innrain 52a, A-6020 Innsbruck, Austria

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

Abstract - The 14-*O*-benzyl derivatives of cyprodime and 3-hydroxycyprodime (compounds (**5**) and (**6**), respectively) were synthesized in several steps from 3-desoxynaltrexone (**2a**) and naltrexone (**2**), respectively. In the mouse vas deferens preparation it was found that a 14-*O*-benzyl group could enhance μ opioid receptor affinity in cyprodime while the μ affinity of 3-hydroxycyprodime was not changed.

Opioid antagonists have been indispensable as tools in opioid research. For example, the chief criterion for the classification of an agonist effect as being opioid receptor mediated is the ability of known opioid antagonists naloxone (**1**) and naltrexone (**2**) to reversibly antagonize this effect in a competitive fashion. The usefulness of naloxone and naltrexone for this purpose stems from the fact that they are universal opioid antagonists; that is, they are capable of antagonizing the agonist effects mediated by multiple opioid receptor types.

In addition to their uses as pharmacological tools, selective, non-peptide opioid antagonists have been described as having potential clinical applications in the treatment of a variety of disorders where endogenous opioids play a modulatory role. These include for instance disorders of food intake, shock, constipation, mental disorders, CNS injury, alcoholism, drug addiction and immune function (immune stimulation or suppression).[2]

Cyprodime (**3**) was found to be a pure opioid antagonist with high selectivity for μ receptors and has become a valuable tool in opioid research.[3] Introduction of a 3-OH group to the cyprodime molecule resulted in a compound (**4**, 3-hydroxycyprodime) which exhibited higher μ receptor affinity than

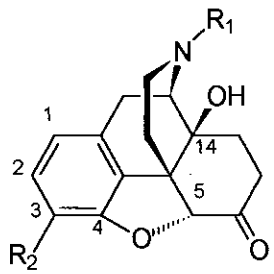
[#] This paper is dedicated to Dr. Bernhard Witkop on the occasion of his 80th birthday.

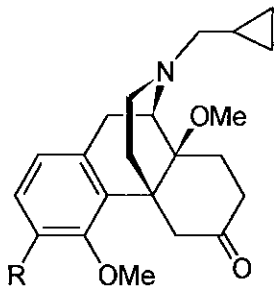
[Δ] Present address: Department of Pharmacology, University of Michigan, Ann Arbor, MI 48109, U. S. A.

cyprodime and retaining antagonist purity and selectivity in the mouse vas deferens preparation (MVD) while in the guinea pig ileum preparation (GPI) not only μ receptor affinity was enhanced but also κ affinity was increased.[4]

Here we report on the synthesis and pharmacological evaluation of novel 14-O-benzyl substituted analogues of cyprodime (compounds (**5**) and (**6**)).

Figure





1 R_1 = allyl, R_2 = OH

2 R_1 = cyclopropylmethyl, R_2 = OH

2a R_1 = cyclopropylmethyl, R_2 = H

3 R = H

4 R = OH

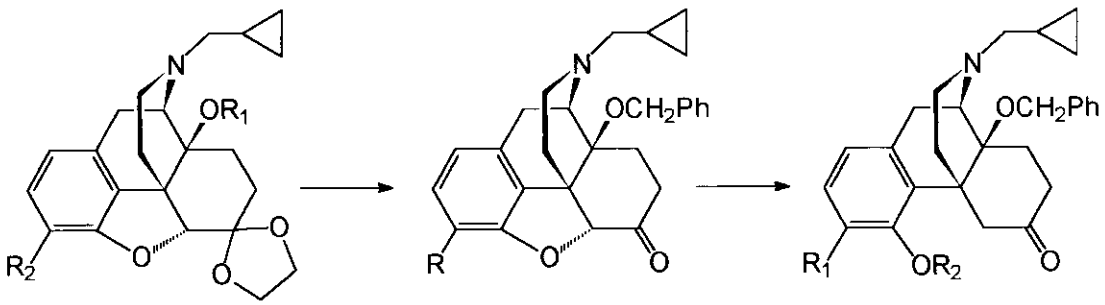
RESULTS AND DISCUSSION

Synthesis

The synthesis of cyprodime analogue (**5**) started from 3-desoxynaltrexone (**2a**) which is readily prepared from naltrexone in two steps.[5] Prior to 14-*O*-alkylation the ketal (**7**) was formed, which was treated with benzyl bromide in DMF using NaH as base to give 14-*O*-benzylated derivative (**8**). Acid hydrolysis of the ketal function afforded morphinanone (**9**). Reductive cleavage of the 4,5-oxygen bridge with Zn and NH_4Cl in refluxing MeOH gave phenol (**10**), which was 4-*O*-methylated with phenyltrimethylammonium chloride (Rodionov reagent) in DMF in the presence of potassium carbonate to yield 14-*O*-benzyl substituted cyprodime (**5**).

The 3-hydroxycyprodime analogue (**6**) was prepared starting from naltrexone (**2**). After ketalization, compound (**11**) was 3,14-bis-*O*-benzylated with benzyl bromide in DMF employing NaH as base to give ketal (**12**), which was hydrolized to afford ketone (**13**). The 4,5-oxygen bridge was opened reductively as described above to give phenol (**14**), which was methylated using Rodionov reagent to yield 3-*O*-protected derivative (**15**). Catalytic hydrogenation over Pd/C afforded 14-*O*-benzylated 3-hydroxycyprodime (**6**).

Scheme



7 $R_1 = R_2 = H$
8 $R_1 = CH_2Ph$, $R_2 = H$
11 $R_1 = H$, $R_2 = OH$
12 $R_1 = CH_2Ph$, $R_2 = OCH_2Ph$

9 $R = H$
13 $R = OCH_2Ph$

5 $R_1 = H$, $R_2 = Me$
6 $R_1 = OH$, $R_2 = Me$
10 $R_1 = R_2 = H$
14 $R_1 = OCH_2Ph$, $R_2 = H$
15 $R_1 = OCH_2Ph$, $R_2 = Me$

Table

Antagonist K_e Values of Compounds (3) - (6) Determined in the Mouse Vas Deferens Preparation (MVD)

	K_e[a] (nM)			selectivity ratio	
Compound	DAMGO (μ)	U69593 (κ)	DPDPE (δ)	δ/μ	κ/μ
(**5**)	12.3	218	788	64	18
(**6**)	7.08	85	815	115	12
cyprodime (**3**)	55.4	6108	1551	110	28
3-hydroxycyprodime (**4**)	5.62	368	316	56	65
naloxone	1.4	9.6	15.9	7	12
naltrexone	2.3	12.9	12.3	5.3	5.6

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

Pharmacological Evaluation

The novel compounds have been evaluated in MVD as described earlier.[3,4] Introduction of a 14-*O*-benzyl group onto cyprodime (compound (**5**)) enhanced μ affinity *ca.* 4-fold, but this was accompanied by a 29-fold increase in κ affinity, leading to a decrease in selectivity. A 14-benzyloxy group instead of a 14-methoxy group in 3-hydroxycyprodime (compound (**6**)) did not alter the μ affinity of **4**, and increased κ affinity by 4-fold and decreased δ affinity by 2.5-fold resulting in a high δ/μ selectivity ratio and a lower κ/μ selectivity ratio. It is noticeable that the introduction of a 14-*O*-benzyl substituent into compounds (**3**) and (**4**) improves κ receptor recognition (Table).

EXPERIMENTAL

General Details

Melting points: *Kofler* melting-point microscope; uncorrected. Optical rotations: *c* in g/100 mL; *Perkin-Elmer-141* polarimeter. IR Spectra: in cm^{-1}; *Shimadzu IR-470* apparatus. ^{1}H-NMR Spectra: *Varian Gemini 200* spectrometer; δ in ppm rel. to $SiMe_4$ as internal reference, *J* in Hz. MS spectra: *Finnigan MAT 44S* apparatus. Elemental Analyses were performed at the Institute of Physical Chemistry of the University of Vienna.

17-Cyclopropylmethyl-4,5α-epoxy-14-hydroxymorphinan-6-spiro-2′-dioxolane (7). A solution of **2a** (8.0 g, 24.58 mmol) and CH_3SO_3H (3.5 ml, 54.01 mmol) in 180 mL of ethylene glycol was stirred at 80 - 90° C (bath temp.) for 15 h under N_2. After addition of 250 mL of H_2O and alkalization with conc. NH_4OH, the mixture was extracted with CH_2Cl_2 (1 x 100 mL, 3 x 30 mL). The combined organic layers were washed with H_2O (2 x 250 mL) and brine (100 mL), dried (Na_2SO_4) and evaporated. The residue (8.79 g brownish crystals) were treated with refluxing MeOH (10 mL) to yield 8.21 g (90%) of **7** as slightly pink crystals. A small portion was recrystallized from MeOH to obtain an analytical sample: mp 180 - 181° C; IR (KBr): 3414 (OH) cm^{-1}; ^{1}H-NMR (300.13 MHz) ($CDCl_3$): δ 7.04 (t, J = 7.8 Hz, C2-H), 6.64 (d, J = 7.8 Hz, C1-H), 6.58 (d, J = 7.8 Hz, C3-H), 5.17 (s, 1 H, OH), 4.51 (s, 1 H, C5-H), 4.17 - 3.69 (m, 4 H, C6-$(OCH_2)_2$); MS (CI): m/z 370 (M^++1); Anal. Calcd for $C_{22}H_{27}NO_4$.0.1 MeOH: C 71.23, H 7.41, N 3.76. Found: C 71.15, H 7.41, N 3.78.

14-Benzyloxy-17-cyclopropylmethyl-4,5α-epoxymorphinan-6-spiro-2′-dioxolane (8). A mixture of **7** (7.7 g, 20.84 mmol), NaH (1.86 g, 77.50 mmol; obtained from 3.10 g of 60% NaH dispersion in oil by

washings with petroleum ether), and 100 mL of anhydrous DMF was stirred under N_2 at 0 – 5° C for 15 min. Benzyl bromide (3.7 mL, 31.15 mmol) was added dropwise within 10 min and the resulting mixture was stirred for 3 h (1 h at 0 - 5° C, 2 h at rt). Excess NaH was destroyed carefully by addition of small pieces of ice. The mixture was poured into 250 mL of H_2O and extracted with CH_2Cl_2 (1 x 150 mL, 2 x 50 mL). The combined organic layers were washed with H_2O (3 x 300 mL), dried over Na_2SO_4 and evaporated. The residue (10.16 g, yellow oil) was crystallized from MeOH to give 8.58 g (90%) colorless crystals of **8** . A small portion was recrystallized from MeOH for analyses: mp 117 -119° C; ^{1}H-NMR ($CDCl_3$): δ 7.48 - 7.26 (m, 5 arom. H), 7.04 (t, J = 7.8 Hz, C2- H), 6.66 (d, J = 7.3 Hz, C1-H), 6.59 (d, J = 7.8 Hz, C3- H), 4.77 (d, J = 10.3 Hz, 1H, OCH_2Ph), 4.54 (s, 1H, C5-H), 4.27 (d, J = 10.3 Hz, 1H, OCH_2Ph), 4.16 - 3.69 (m, 4 H, C6-$(OCH_2)_2$); MS (CI): m/z 460 (M^++1); Anal. Calcd for $C_{29}H_{33}NO_4$: C 75.79, H 7.24, N 3.05. Found: C 75.69 H 7.51 N 3.11.

14-Benzyloxy-17-cyclopropylmethyl-4,5α-epoxymorphinan-6-one (9). A solution of **8** (8.25 g, 17.95 mmol) in MeOH (140 mL) / H_2O (175 mL / conc. HCl (35 mL) was refluxed for 4 h. After cooling with ice, the solution was alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (1 x 100 mL, 2 x 25 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue (7.07 g, colorless foam, 95%) was pure on TLC and was used for the next synthetic step without further purification: IR (KBr): 1726 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.51 - 7.27 (m, 5 arom. H), 7.06 (ps-t, C2-H), 6.73 (d, J = 8.3 Hz, C1- H), 6.69 (d, J = 7.8 Hz, C3- H), 4.91 (d, J = 10.3 Hz, 1H, OCH_2Ph), 4.62 (s, 1 H, C5-H), 4.37 (d, J = 10.3 Hz, 1H, OCH_2Ph); ^{13}C-NMR ($CDCl_3$): δ 208.9 (C6), 133.9 (C12), 129.0, 128.3, 127.8, 127.4 (5 arom. CH-C), 128.1 (C11), 118.5 (C1), 107.9 (C2), 89.8 (C5), 75.9 (C14), 56.1 (C9), 9.4 (tert. cyclopropyl-C), 3.9, 3.8 (2 sec. cyclopropyl-C); MS (CI): m/z 416 (M^++1).

14-Benzyloxy-17-cyclopropylmethyl-4-hydroxymorphinan-6-one (10). Activated Zn powder (3.0 g, 45.89 mmol) was added in portions to a refluxing mixture of **9** (6.0 g, 14.44 mmol), NH_4Cl (6.0 g, 112.17 mmol) and 70 mL of MeOH within 5 min. After stirring and refluxing for 1.5 h, the mixture was filtered, the filtrate evaporated, the residue alkalized with conc. NH_4OH and extracted and with CH_2Cl_2 / MeOH (3 : 1) (1 x 120 mL, 2 x 90 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue (7.07 g, slightly brown foam, 90%) was pure on TLC and was used for the next synthetic step without further purification: IR (KBr): 1699 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.51 -7.25 (m, 5arom. H), 6.91 (ps-t, J = 7.8 Hz, C2- H), 6.71 (d, J = 7.3 Hz, C1- H), 6.58 (d, J = 7.3 Hz, C3- H), 4.96 (d, J = 10.5 Hz, 1H, OCH_2Ph), 4.47 (d, J = 10.5 Hz, 1H, OCH_2Ph); ^{13}C-NMR ($CDCl_3$): δ 215.8 (C6), 128.2, 127.2, 127.1 (5 arom. CH-C), 118.9 (C1), 114.7 (C2), 74.4 (C14), 53.3 (C9), 9.5 (tert. cyclopropyl-C), 3.9 (2 sec. cyclopropyl-C); MS (CI): m/z 418 (M^++1).

14-Benzyloxy-17-cyclopropylmethyl-4-methoxymorphinan-6-one Hydrochloride (5.HCl). A mixture of **10** (4.70 g, 11.26 mmol), phenyltrimethylammonium chloride (6.96 g, 40.54 mmol), K_2CO_3 (7.78 g, 56.29 mmol) and 90 mL of anhydrous DMF was stirred at 80° C (bath temp.) for 7 h. The inorganic material was filtered off, the filtrate evaporated, the oily residue dissolved in CH_2Cl_2 (100 mL), washed with H_2O (3 x 150 mL), dried over Na_2SO_4 and evaporated. The residue (4.93 g, brownish oil) was dissolved in 2 N HCl (100 mL) / MeOH (10 mL), the pH adjusted to 6 with conc. NH_4OH, and extracted with cyclohexane (3 x 50 mL). The aqueous layer was alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue (3.4 g, slightly red oil) was dissolved in Et_2O and treated with Et_2O/HCl to yield 3.41 g (92%) of **5.HCl**: mp 208 - 212° C (decomp); IR (KBr): 3416 ($^+$NH), 1717 (CO) cm^{-1}; ^{1}H-NMR (199.975 MHz) (DMSO-d_6): δ 8.73 (s, 1 H, $^+$NH), 7.58-7.33 (m, 5 arom. H), 7.25 (ps-t, J = 8.0 Hz, C2-H), 6,88 (ps-t, C1-H and C3-H), 4.75 (s, 2 H, OCH_2Ph), 3.78 (s, 3 H, OCH_3); MS (CI): m/z 432 (M^++1); $[\alpha]_D^{20}$ = -65.5° (c 1.05; MeOH); Anal. Calcd for $C_{28}H_{34}NO_3Cl.0.6\ H_2O$: C 70.23, H 7.41, N 2.93, Cl 7.40. Found: C 70.23, H 7.38, N 2.96, Cl 7.47

17-Cyclopropylmethyl-4,5α-epoxy-3,14-dihydroxymorphinan-6-spiro-2′-dioxolane (11). A solution of naltrexone.HCl (9.0 g, 23.82 mmol) und CH_3SO_3H (1.85 mL, 28.55 mmol) in 110 mL of ethylene glycol was stirred at 80 - 90° C (bath temp.) for 15 h. After addition of 250 mL of H_2O and alkalization with conc. NH_4OH, the mixture was extracted with CH_2Cl_2 (1 x 75 mL, 2 x 20 mL). The combined organic layers were washed with H_2O (2 x 250 mL), dried over Na_2SO_4 and evaporated. The residue (8.53 g, slightly gray crystals) was treated with boiling MeOH to give 8.27 g (90%) of **11**. An analytical sample was obtained by recrystallization of a small sample: mp 224 - 226° C; IR (KBr): 3266 and 3235 (OH) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 6.68 (d, J = 8.0 Hz, 1 arom. H), 6.52 (d, J = 8.0 Hz, 1 arom. H), 5.11 (s, 1 H, C14-OH), 4.57 (s, 1 H, C5-H), 4.16 - 3.77 (m, 4 H, C6-$(OCH_2)_2$); MS (CI): m/z 386 (M^++1); Anal. Calcd for $C_{22}H_{27}NO_5.0.2$ MeOH: C 68.04, H 7.15, N 3.57. Found: C 68.13, H 6.89, N 3.52.

3,14-Dibenzyloxy-17-cyclopropylmethyl-4,5α-epoxymorphinan-6-spiro-2′-dioxolane (12). A mixture of **11** (9.3 g, 24.13 mmol), NaH (4.06 g, 169 mmol; obtained from 6.76 g of 60% NaH dispersion in oil by washings with petroleum ether), and 100 mL of anhydrous DMF was stirred under N_2 at 0 – 5° C for 25 min. Benzyl bromide (8.6 mL, 72.4 mmol) was added dropwise within 15 min and the resulting mixture was stirred for 3 h (1 h at 0 – 5° C, 2 h at rt). Excess NaH was destroyed carefully by addition of small pieces of ice. The mixture was poured into 500 mL of H_2O and extracted with CH_2Cl_2 (1 x 250 mL, 2 x 150 mL). The combined organic layers were washed with H_2O (3 x 300 mL), dried over Na_2SO_4 and evaporated. The residue (14.15 g, yellow oil) was crystallized from MeOH (50 mL) to give 10.93 g (80%) colorless crystals of **12**. A small portion was recrystallized from MeOH for analyses: mp 146 - 148° C; ^{1}H-

NMR ($CDCl_3$): δ 7.48 -7.25 (m, 10 arom. H); 6.75 (d, J = 8.0 Hz, 1 arom. H); 6.55 (d, J = 8.0 Hz, 1 arom. H); 5.18 (d, J = 12.2 Hz, 1 H, C3-OCH_2Ph), 5.10 (d, J = 12.2 Hz, 1 H, C3-OCH_2Ph); 4.76 (d, J = 10.3 Hz, 1 H, C14-OCH_2Ph); 4.60 (s, 1 H, C5-H); 4.26 (d, J = 10.3 Hz, 1 H, C14-OCH_2Ph); 4.18 - 3.72 (m, 4 H, C6-$(OCH_2)_2$); MS (CI): m/z 566 (M^++1); Anal. Calcd for $C_{36}H_{39}NO_5$.0.2 MeOH : C 76.00, H 7.01, N 2.45. Found: C 76.08, H 6.92, N 2.45.

3,14-Dibenzyloxy-17-cyclopropylmethyl-4,5α-epoxymorphinan-6-one (13). A solution of **12** (10.0 g, 17.68 mmol) in MeOH (200 mL) / H_2O (250 mL) / conc. HCl (50 mL) was refluxed for 4 h. After cooling with ice, the solution was alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (1 x 100 mL, 2 x 25 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue (8.48 g, slightly brown foam) was purified by column chromatography (silica gel, 230 - 400 mesh, elution with CH_2Cl_2/MeOH/conc. NH_4OH 90 : 9 : 1) to yield 6.28 g (69%) of pure **13** as a colorless foam which was used for the next synthetic step without further purification: IR ($CHCl_3$):1724 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.51 - 7.26 (m, 10 arom. H), 6.71 (d, J = 7.8 Hz, 1 arom. H), 6.56 (d, J = 7.8 Hz, 1 arom. H), 5.28 (d, J = 12.2 Hz, 1 H, C3-OCH_2Ph), 5.20 (d, J = 12.2 Hz, 1 H, C3-OCH_2Ph), 4.91 (d, J = 9.8 Hz, 1 H, C14-OCH_2Ph), 4.67 (s, 1 H, C5-H), 4.37 (d, J = 9.8 Hz, 1 H, C14-OCH_2Ph); ^{13}C-NMR ($CDCl_3$): δ 208.2 (C6), 130.0 (C12), 128.3, 127.8, 127.4 (10 arom. CH-C), 126.3 (C11), 119.3(C1), 118.1 (C2), 90.4 (C5), 76.0 (C14), 72.2 ($PhCH_2OAr$), 56.1 (C9), 9.4 (tert. cyclopropyl-C), 3.9, 3.8 (2 sec. cyclopropyl-C); MS (CI): m/z 522 (M^++1).

3,14-Dibenzyloxy-17-cyclopropylmethyl-4-hydroxymorphinan-6-one (14). Activated Zn powder (2.35 g, 35.94 mmol) was added in portions to a refluxing mixture of **13** (4.5 g, 8.63 mmol), NH_4Cl (4.7 g, 87.87 mmol) and 250 mL of MeOH within 5 min. After stirring and refluxing for 2.5 h, the mixture was filtered, the filtrate evaporated, the residue alkalized with conc. NH_4OH and extracted and with CH_2Cl_2 / MeOH (3 : 1) (5 x 80 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue (4.21 g, slightly red foam, 90%) was pure on TLC and was used for the next synthetic step without further purification: IR (KBr): 3501 (OH) 1709 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.50 - 7.28 (m, 10 arom. H), 6.73 (d, J = 8.5 Hz, 1 arom. H), 6.55 (d, J = 8.5 Hz, 1 arom. H), 5.02 (s, 2 H, C3-OCH_2Ph), 4.92 (d, J = 10.7 Hz, 1 H, C14-OCH_2Ph), 4.44 (d, J = 10.7 Hz, 1 H, C14-OCH_2Ph); ^{13}C-NMR ($CDCl_3$): δ 211.9 (C6), 130.5 (C12), 128.6, 128.2, 127.7, 127.3, 127.1 (10 arom. CH-C), 125.3 (C11), 118.1 (C1), 110.4 (C2), 74.2 (C14) 71.4 ($PhCH_2OAr$), 53.3 (C9), 9.5 (tert. cyclopropyl-C), 3.8 (2 sec. cyclopropyl-C); MS (CI): m/z 524 (M^++1).

3,14-Dibenzyloxy-17-cyclopropylmethyl-4-methoxymorphinan-6-one (15). A mixture of **14** (3.75 g, 7.16 mmol), phenyltrimethylammonium chloride (4.42 g, 25.75 mmol), K_2CO_3 (4.95 g, 35.82 mmol) and

80 mL of anhydrous DMF was stirred at 80° C (bath temp.) for 5 h. The inorganic material was filtered off, the filtrate evaporated, the oily residue dissolved in CH_2Cl_2 (70 mL), washed with H_2O (3 x 80 mL), dried over Na_2SO_4 and evaporated. The residue (3.65 g, brownish oil) was dissolved in 2 N HCl (80 mL) / MeOH (8 mL), the pH adjusted to 6 with conc. NH_4OH, and extracted with cyclohexane (3 x 40 mL). The aqueous layer was alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3 x 40 mL). The combined organic layers were washed with H_2O, dried over Na_2SO_4 and evaporated. The residue (3.4 g, slightly red oil) was pure on TLC and used for the next synthetic step without further purification: IR ($CHCl_3$): 1705 (CO) cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 7.49 - 7.28 (m, 10 arom. H), 6.79 (d, J = 8.5 Hz, 1 arom. H), 6.72 (d, J = 8.5 Hz, 1 arom. H), 5.03 (s, 2 H, C3-OCH_2Ph), 4.91 (d, J = 10.5 Hz, 1 H, C14-OCH_2Ph), 4.43 (d, J = 10.5 Hz, 1 H, C14-OCH_2Ph), 3.93 (s, 3 H, C4-OCH_3); ^{13}C-NMR ($CDCl_3$): δ 211.6 (C6), 130.3 (C12), 128.5, 128.2, 127.4, 127.3 (10 arom. CH-C), 122.5 (C1), 113.6 (C2), , 74.3 (C14), 71.1 ($PhCH_2OAr$), 60.6 (OCH_3), , 53.2 (C9), 9.5 (tert. cyclopropyl-C), 3.9 (2 sec. cyclopropyl-C); MS (CI): m/z 538 (M^++1).

14-Benzyloxy-17-cyclopropylmethyl-3-hydroxy-4-methoxymorphinan-6-one Hydrobromide (6.HBr). A mixture of **15** (2.64 g, 4.91 mmol), 750 mg of 10% Pd/C catalyst and 100 mL of MeOH was hydrogenated at 40 psi for 1 h. The catalyst was filtered off and the filtrate evaporated. The residue (1.99 g, yellowish foam) was dissolved in a small quantity of EtOH and treated with 48% HBr to yield 1.92 g (84%) of **6.HBr**: mp > 210° C (decomp); IR (KBr): 3418 ($^+$NH), 3169 (OH), 1717 (CO) cm^{-1}; ^{1}H-NMR (DMSO-d_6): δ 9.40 (s, 1 H, OH), 8.45 (s, 1 H, $^+$NH), 7.54 - 7.33 (m, 5 arom. H), 6.84 (d, J = 8.4 Hz, 1 arom. H), 6.79 (d, J = 8.4 Hz, 1 arom. H), 4.79 (d, J = 11.7 Hz, 1 H, , C14-OCH_2Ph), 4.69 (d, J = 11.7 Hz, 1 H, , C14-OCH_2Ph), 3.82 (s, 3 H, C4-OCH_3); MS (CI): m/z 448 (M^++1); $[\alpha]_D^{20}$ = -67.1° (c 1.04; MeOH); Anal. Calcd for $C_{28}H_{34}NO_4Br$: C 63.64, H 6.48, N 2.65, Br 15.12. Found: C 63.52, H 6.67, N 2.58, Br 15.06.

REFERENCES

1. H. Schmidhammer, R. Krassnig, E. Greiner, J. Schütz, A. White, and I. P. Berzetei-Gurske, *Helv. Chim. Acta*, 1998, **81**, 1064.
2. P. S. Portoghese, *J. Med. Chem.*, 1991, **34**, 1757; H. Schmidhammer, in "Progress in Medicinal Chemistry", ed.by. G. Ellis, D. K. Luscombe, A. W. Oxford, 1998, Vol. 35, in press.
3. H. Schmidhammer, W. P. Burkard, L. Eggstein-Aeppli, and C. F. C. Smith, *J. Med. Chem.*, 1989, **32**, 418; H. Schmidhammer, C. F. C. Smith, D. Erlach, M. Koch, R. Krassnig, W. Schwetz, and C. Wechner, *J. Med. Chem.*, 1990, **33**, 1200; F. Ötvös, G. Tóth, and H.Schmidhammer, *Helv. Chim. Acta*, 1992, **75**, 1718; R. Krassnig and H. Schmidhammer, *Heterocycles*, 1994, **38**, 877;

H. Schmidhammer, *Current Topics in Med. Chem.*, 1993, **1**, 261.

4. H. Schmidhammer, H. K. Jennewein, R. Krassnig, J. R. Traynor, D. Patel, K. Bell, G. Froschauer, K. Mattersberger, C. Jachs-Ewinger, P. Jura, G. L. Fraser, and V. N. Kalinin, *J. Med. Chem.*, 1995, **38**, 3071.
5. R. Krassnig and H. Schmidhammer, *Heterocycles*, 1994, **38**, 877.

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