A NEW AND EFFICIENT SYNTHESIS OF THE μ-SELECTIVE OPIOID ANTAGONIST CYPRODIME

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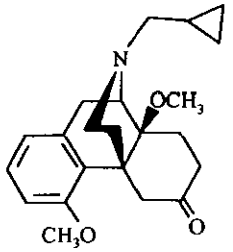
Abstract - The μ-selective opioid antagonist cyprodime has been prepared in a six-step sequence starting from naltrexone. The 3-hydroxy group of naltrexone was removed *via* tetrazolyl ether (**3**) which was hydrogenated catalytically to give 17-cyclopropylmethyl-4,5α-epoxy-14-hydroxymorphinan-6-one (**4**). Methylation gave 17-cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-6,14-dimethoxymorphinan (**5**) and hydrolysis of it 17-cyclopropylmethyl-4,5α-epoxy-14-methoxymorphinan-6-one (**6**). Reductive opening of the 4,5-epoxy bridge and methylation of the resulting phenol (**7**) yielded cyprodime (**1**).

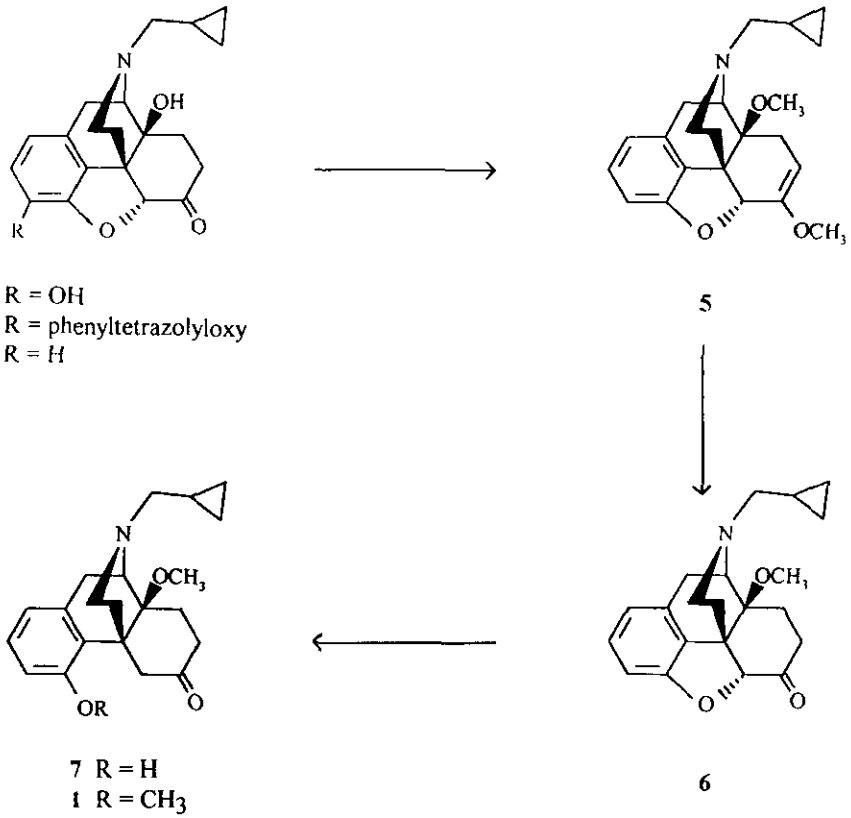
Cyprodime (**1**) is a pure opioid antagonist with high selectivity for μ receptors.[1] Since cyprodime has the highest μ-selectivity of nonpeptide, competitive μ opioid antagonists reported, this ligand is being used as biological and pharmacological tool in opioid research. For instance in bioassays[2] and to characterize cloned and expressed opioid receptors.[3] It has also been recently tritium labelled.[4] Cyprodime has been originally prepared in nine steps starting from rather expensive oxymorphone.[1] A lengthy but more efficient route involved ten steps starting from thebaine.[2] Thus we sought for a shorter and more useful access to cyprodime.



Cyprodime (**1**)

RESULTS AND DISCUSSION

The tetrazolyl ether (**3**) was formed by reaction of naltrexone·HCl with 5-chloro-1-phenyl-1*H*-tetrazole.[5] Catalytic hydrogenation in glacial acetic acid over Pd/C-catalyst afforded 3-desoxynaltrexone (**4**). Alkylation of **4** with 2.75 equivalents of dimethyl sulfate at 0° C in the presence of an excess of sodium hydride in DMF yielded the enol ether (**5**) (monomethylation of the oxygen in position 14 was not possible). Hydrolysis with conc. HCl in MeOH gave the known morphinanone (**6**).[2] Further conversion into cyprodime was accomplished as published earlier.[2] Thus, the 4,5-oxygen bridge of **6** was cleaved with activated zinc and ammonium chloride in refluxing methanol to yield the phenol (**7**), which was *O*-methylated with phenyltrimethylammonium chloride in DMF in the presence of potassium carbonate to give cyprodime (**1**).



2 R = OH
3 R = phenyltetrazolyloxy
4 R = H

5

7 R = H
1 R = CH_3

6

EXPERIMENTAL

General. Melting points were determined with a Kofler melting point microscope and are uncorrected. Ir spectra were recorded on a Galaxy FTIR 3000. ^{1}H Nmr were performed on a Bruker AM 300 (300 MHz) and are reported in parts per million (J = apparent coupling constant in Hz). Chemical ionisation mass spectra (CI-ms) were obtained from a Finnigan MAT 44S apparatus. Elemental analyses were performed by Mag. J. Theiner at the Institute of Physical Chemistry, University of Vienna. Naltrexone·HCl was purchased from Mallinckrodt Speciality Chemicals Company, St. Louis, MO 63147, USA.

17-Cyclopropylmethyl-4,5α-epoxy-14-hydroxy-3-[(1-phenyl-1*H*-tetrazol-5-yl)oxy]-morphinan-6-one (3). A mixture of naltrexone·HCl (7.0 g, 18.52 mmol), 5-chloro-1-phenyl-1*H*-tetrazole (3.65 g, 20.21 mmol), K_2CO_3 (7.0 g, 50.65 mmol), and 35 ml of anhydrous DMF was stirred at room temperature for 20 h. After addition of 500 ml of H_2O, the mixture was extracted with CH_2Cl_2 (2 x 100 ml, 1 x 50 ml). The combined organic layers were washed with H_2O (3 x 500 ml) and brine (100 ml), dried (Na_2SO_4), and evaporated. The residue (9.29 g brownish foam) was crystallized with 15 ml of EtOH to yield 8.87 g (99%) of **3**. A small portion of this material was recrystallized from MeOH to give an analytical sample, mp 145 - 146° C. Ir (KBr): 1724 (CO) cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 7.88 - 7.45 (m, 5 arom. H), 7.15 (d, J = 8.5 Hz, 1 arom. H), 6.73 (d, J = 8.5 Hz, 1 arom. H), 5.23 (s, 1 H, OH), 4.70 (s, 1 H, C_5-H). CI-ms: m/z 486 (M^+ + 1). Anal. Calcd for $C_{27}H_{27}N_5O_4$ · 0.7 MeOH: C 65.50, H 5.91, N 13.79. Found: C 65.29, H 5.69, N 14.15.

17-Cyclopropylmethyl-4,5α-epoxy-14-hydroxymorphinan-6-one (4). A mixture of **3** (8.5 g, 17.51 mmol), 10% Pd/C-catalyst (3.3 g), and 120 ml of glacial acetic acid was hydrogenated at 40° C for 17 h. The catalyst was filtered off and the filtrate was evaporated to give a light brown crystalline residue which was alkalized with conc. NH_4OH and extracted with CH_2Cl_2 (3 x 75 ml). The combined organic layers were washed with H_2O (3 x 100 ml), dried (Na_2SO_4), and evaporated to afford a slightly brown oil. Crystallization with MeOH (10 ml) yielded 4.51 g (79%) of **4** as colorless crystals. An analytical sample was obtained by recrystallization from MeOH, mp 148 - 149° C. Ir (KBr): 1726 (CO) cm^{-1}. ^{1}H Nmr ($CDCl_3$): δ 7.05 (t, J = 7.8 Hz, 1 arom. H), 6.73 (d, J = 7.8 Hz, 1 arom. H), 6.67 (d, J = 7.8 Hz, 1 arom. H), 5.17 (s, 1 H, OH), 4.61 (s, 1 H, C_5-H). CI-ms: m/z 326 (M^+ + 1). Anal. Calcd for $C_{20}H_{23}NO_3$: C 73.82, H 7.12, N 4.30. Found: C 73.69, N 7.23, N 4.21.

17-Cyclopropylmethyl-6,7-didehydro-4,5α-epoxy-6,14-dimethoxymorphinan (5). To a stirred solution of **4** (2.5 g, 7.68 mmol) in 20 ml of anhydrous DMF was added NaH (1.65 g, 68.75 mmol; obtained

from 2.75 g 60% NaH dispersion by washing with PE) under N_2. The resulting mixture was cooled to 0 - 5° C for 15 min, then dimethyl sulfate (2.0 ml, 21.12 mmol) was added and stirring at 0 - 5° C was continued for 1 h. Excess NaH was destroyed carefully with small pieces of ice, then the mixture was poured on 100 ml H_2O. After extractions with CH_2Cl_2 (1 x 100 ml, 2 x 50 ml), the combined organic layers were washed with H_2O (3 x 150 ml), dried (Na_2SO_4), and evaporated to yield 2.53 g of a slightly yellow crystalline residue. Treatment with boiling EtOH gave 1.94 g (71%) of **5** as colorless crystals. An analytical sample was prepared by recrystallization of a small portion from MeOH, mp 167 - 170° C. ^1H Nmr ($CDCl_3$): δ 7.02 (t, J = 7.8 Hz, 1 arom. H), 6.63 (dd, J = 7.8, 7.8 Hz, 2 arom. H), 4.82 (s, 1 H, C_5-H), 3.50 (s, 3 H, C_6-OCH_3), 3.30 (s, 3 H, C_{14}-OCH_3). CI-ms: m/z 354 (M^+ + 1). Anal. Calcd for $C_{22}H_{27}NO_3 \cdot 0.3$ MeOH: C 73.77, H 7.83, N 3.86. Found: C 73.84, H 7.45, N 3.89.

17-Cyclopropylmethyl-4,5α-epoxy-14-methoxymorphinan-6-one (6). A solution of **5** (1.5 g, 4.24 mmol) in MeOH (18 ml) and conc. HCl (2 ml) was refluxed for 1 h and then evaporated. The oily residue was dissolved in H_2O, alkalized with conc. NH_4OH, and extracted with CH_2Cl_2 (3 x 15 ml). The combined organic layers were washed with H_2O (2 x 30 ml), dried over Na_2SO_4 and evaporated. The resulting residue (1.42 g yellow oil) was crystallized with MeOH to yield 1.15 g (80%) of **6**. Recrystallization of a small portion provided pure **6**, mp 140 - 143° C (lit.,[2] mp 140 - 142° C). This compound was identical with an authentic sample of **6** by mixed mp, ir, and ^1H nmr.

17-Cyclopropylmethyl-4-hydroxy-14-methoxymorphinan-6-one (7). Activated Zn powder (1.38 g, 21.1 mmol) was added to a refluxing mixture of **6** (690 mg, 2.03 mmol), NH_4Cl (1.38 g, 25.8 mmol), and 25 ml of MeOH within 5 min. This mixture was stirred and refluxed for another 40 min. The inorganic material was filtered off, the filtrate evaporated, the residue alkalized with conc. NH_4OH and extracted with CH_2Cl_2/MeOH (3 : 1) (5 x 15 ml). The combined organic layers were washed with H_2O and brine, dried (Na_2SO_4), and evaporated to give a slightly brown foam (700 mg) which was crystallized from MeOH to yield 540 mg (78%) of **7**, mp 186 - 190° C (lit.,[2] mp 188 - 191° C). This compound was identical with an authentic sample of **7** by mixed mp, ir, and ^1H nmr.

17-Cyclopropylmethyl-4,14-dimethoxymorphinan-6-one (Cyprodime; 1). A mixture of **7** (540 mg, 1.58 mmol), phenyltrimethylammonium chloride (840 mg, 4.89 mmol), K_2CO_3 (800 mg, 5.79 mmol), and 25 ml of anhydrous DMF was stirred at 80° C (bath temperature) for 6.5 h. The inorganic material was filtered off and the filtrate was evaporated. The oily residue was dissolved in CH_2Cl_2 (25 ml), washed with

H_2O (3 x 30 ml), dried (Na_2SO_4), and evaporated to give 500 mg of a yellowish crystalline residue. Recrystallization from MeOH afforded 377 mg (67%) of pure **1**, mp 155 - 160° C (lit.,[2] mp 155 - 159°C). This compound was identical with an authentic sample of **1** by mixed mp, ir, and ^1H nmr.

ACKNOWLEDGEMENT

We wish to thank Prof. Dr. K.-H. Ongania for performing the mass spectra and Mag. W. Mühlecker for recording the ^1H nmr spectra.

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Received, 17th December, 1993