A NEW AND EFFICIENT SYNTHESIS OF THE μ OPIOID RECEPTOR ANTAGONISTS 14-*O*-METHYL- AND 14-*O*-ETHYLNALOXONE AND -NALTREXONE#

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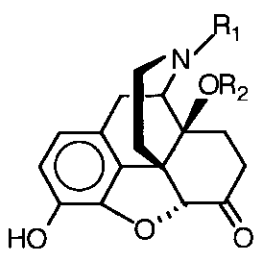
Abstract - The μ opioid receptor antagonists 14-*O*-methyl- and 14-*O*-ethylnaloxone (**3** and **4**, respectively) and 14-*O*-methyl- and 14-*O*-ethylnaltrexone (**5** and **6**, respectively) have been prepared in a three-step sequence starting from either naloxone (**1**) or naltrexone (**2**). The 3-hydroxy group of **1** and **2** was protected with a benzyl group prior to 14-*O*-alkylation with either dimethyl or diethyl sulfate to give the enol ethers (**9** - **12**). Acid hydrolysis afforded compounds (**3** - **6**).

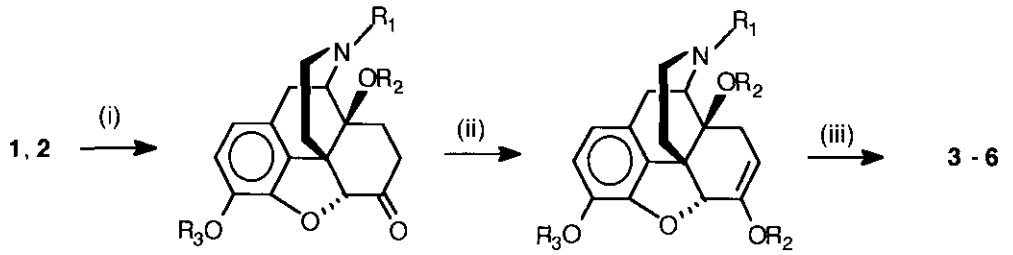
The 14-*O*-methyl and 14-*O*-ethyl ethers of the opioid antagonists naloxone (**1**) and naltrexone (**2**), compounds (**3** - **6**), have been prepared in six steps starting from 14-hydroxycodeinone and were found to have preference for μ opioid receptors similar to their parent compounds naloxone and naltrexone.[1] Unfortunately the affinity and antagonist potency at κ opioid receptors was not assessed. Since we wanted to compare these compounds biologically and pharmacologically to the μ opioid receptor antagonists cyprodime,[2] 3-hydroxycyprodime[3] and analogues, we prepared compounds (**3** - **6**) starting from naloxone and naltrexone, respectively.



1 R_1 = allyl, R_2 = H
2 R_1 = CPM, R_2 = H
3 R_1 = allyl, R_2 = Me
4 R_1 = allyl, R_2 = Et
5 R_1 = CPM, R_2 = Me
6 R_1 = CPM, R_2 = Et
CPM = cyclopropylmethyl

This paper is dedicated with best wishes to Prof. Dr. K. Nakanishi on the occasion of his 75th birthday and to Prof. Dr. W. Wiegrebe on the occasion of his 65th birthday.

3-*O*-Benzylation of **1** and **2** afforded 3-*O*-benzylnaloxone (**7**)[4,5] and 3-*O*-benzylnaltrexone (**8**),[6,7] respectively. Alkylation with 2.75 equivalents of dimethyl or diethyl sulfate in the presence of an excess of sodium hydride in DMF gave the enol ethers (**9** - **12**).[8-11] Monoalkylation of the oxygen in position 14 is not possible as described earlier.[2,12] The facile conversion of morphinan-6-ones (e. g. naltrexone) to enolic derivatives is obviously due to the greater-than-normal enolic character of the 6-keto group.[13] Acid hydrolysis of the enol ethers yielded the 14-*O*-methyl and 14-*O*-ethyl ethers of naloxone and naltrexone (compounds **3** - **6**),[14-17] respectively.



7 R_1 = allyl, R_2 = H, R_3 = CH_2Ph
8 R_1 = CPM, R_2 = H, R_3 = CH_2Ph
9 R_1 = allyl, R_2 = Me, R_3 = CH_2Ph
10 R_1 = allyl, R_2 = Et, R_3 = CH_2Ph
11 R_1 = CPM, R_2 = Me, R_3 = CH_2Ph
12 R_1 = CPM, R_2 = Et, R_3 = CH_2 Ph

CPM = cyclopropylmethyl

Scheme: Reaction conditions and reagents: (i) $PhCH_2Br$, K_2CO_3, DMF, rt, 24 h; (ii) $(MeO)_2SO_2$ or $(EtO)_2SO_2$, NaH, DMF, 0° C, 1 h; (iii) MeOH/conc. HCl (3:2), reflux, 20 h.

The results of biological and pharmacological testing will be published elsewhere.

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4. All novel compounds showed satisfactory elemental analyses.
5. **7**: mp 126-128° C (MeOH); IR (KBr) 3356 (OH), 1726 (CO) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.47-7.26 (m, 5 arom. H), 6.70 (d, J = 8.2 Hz, 1 arom. H), 6.59 (d, J = 8.2 Hz, 1 arom. H), 5.84 (m, 1 olef. H), 5.33-5.16 (m, 2 olef. H and 2 H, CH_2Ph), 4.68 (s, H-C(5)); CI-MS: m/z 418 (M^++1); $[\alpha]_D^{20}$= -181.5° (c = 0.84, CH_2Cl_2).
6. P. S. Portoghese, M. Sultana, S. T. Moe, and A. E. Takemori, *J. Med. Chem.*, 1994, **37**, 579.
7. **8**: mp 106-107° C (MeOH) (lit.,[6] mp 135-136° C); IR (KBr): 3335 (OH), 1724 (CO) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 7.45-7.26 (m, 5 arom. H), 6.70 (d, J = 8.2 Hz, 1 arom. H), 6.54 (d, J = 8.2 Hz, 1 arom. H), 5.28 (d, J = 12.1 Hz, 1 H, CH_2Ph), 5.19 (d, J = 12.1 Hz, 1 H, CH_2Ph), 4.68 (s, H-C(5)); CI-MS: m/z 432 (M^++1).
8. **9**: mp 93-96° C (MeOH); ^1H NMR(200 MHz, $CDCl_3$): δ 7.42-7.25 (m, 5 arom. H), 6.68 (d, J = 8.2 Hz, 1 arom. H), 6.54 (d, J = 8.2 Hz, 1 arom. H), 5.88 (m, 1 olef. H), 5.28-5.11 (m, 2 olef. H and 2 H, CH_2Ph), 4.88 (s, H-C(5)), 4.56 (m, 1 olef.H, H-C(7)), 3.51 (s, CH_3O-C(6)), 3.24 (s, CH_3O-C(14)); CI-MS: m/z 446 (M^++1); $[\alpha]_D^{20}$= -178.8° (c = 0.90, CH_2Cl_2).
9. **10**: mp 58-61° C (MeOH); ^1H NMR (200 MHz, $CDCl_3$): δ 7.43-7.28 (m, 5 arom. H), 6.66 (d, J = 8.2 Hz, 1 arom. H), 6.52 (d, J = 8.2 Hz, 1 arom. H), 5.82 (m, 1 olef. H), 5.25-5.08 (m, 2 olef. H and 2 H, CH_2Ph), 4.87 (s, H-C(5)), 4.53 (m, 1 olef.H, H-C(7)), 1.30 (t, J = 7.1 Hz, 3 H, OCH_2CH_3) 1.17 (t, J = 6.9 Hz, 3 H, OCH_2CH_3) ; CI-MS: m/z 446 (M^++1); $[\alpha]_D^{20}$= -178.8° (c = 0.90, CH_2Cl_2).
10. **11**: yellowish oil which was not further purified (no elemental analysis was performed); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.27 (m, 5 arom. H), 6.68 (d, J = 8.2 Hz, 1 arom. H), 6.49 (d, J = 8.2 Hz, 1 arom. H), 5.19 (d, J = 12.2 Hz, 1 H, CH_2Ph), 5.13 (d, J = 12.2 Hz, 1 H, CH_2Ph), 4.87 (s, H-C(5)), 4.56 (m, 1 olef.H, H-C(7)), 3.51 (s, CH_3O-C(6)), 3.29 (s, CH_3O-C(14)); CI-MS: m/z 460 (M^++1).
11. **12**: mp 109-112° C (MeOH); ^1H NMR (300 MHz, $CDCl_3$): δ 7.41-7.25 (m, 5 arom. H), 6.68 (d, J = 8.2 Hz, 1 arom. H), 6.48 (d, J = 8.2 Hz, 1 arom. H), 5.17 (d, J = 12.2 Hz, 1 H, CH_2Ph), 5.15 (d, J = 12.2 Hz, 1 H, CH_2Ph) , 4.86 (s, H-C(5)), 4.55 (m, 1 olef.H, H-C(7)), 1.29 (t, J = 7.0 Hz, 3 H, OCH_2CH_3) 1.17 (t, J = 6.9 Hz, 3 H, OCH_2CH_3) ; CI-MS: m/z 488 (M^++1).

12. H. Schmidhammer, L. Aeppli, L. Atwell, F. Fritsch, A. E. Jacobson, M. Nebuchla, and G. Sperk, *J. Med. Chem.*, 1984, **27**, 1575.
13. H. Nagase, A. Abe, and P. S. Portoghese, *J. Org. Chem.*, 1989, **54**, 4120.
14. **3**: mp 194-196° C (MeOH) (lit.,[1] mp 197-199° C, petroleum ether); this compound was identical by mixed melting point, IR, and ^{1}H NMR with an authentic sample.
15. **4**: mp 146-148° C (MeOH) (lit.,[1] mp 146-147° C, diethyl ether/petroleum ether); this compound was identical by mixed melting point, IR, and ^{1}H NMR with an authentic sample.
16. **5**: mp 187-188° C (MeOH) (lit.,[1] mp 187-188° C, petroleum ether); this compound was identical by mixed melting point, IR, and ^{1}H NMR with an authentic sample.
17. **6**: mp 165-167° C (MeOH) (lit.,[1] mp 165-166° C, diethyl ether/petroleum ether); this compound was identical by mixed melting point, IR, and ^{1}H NMR with an authentic sample.

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