161. Synthesis and Biological Evaluation of 14-Alkoxymorphinans

Part 8[1])

14-Methoxymetopon, an Extremely Potent Opioid Agonist

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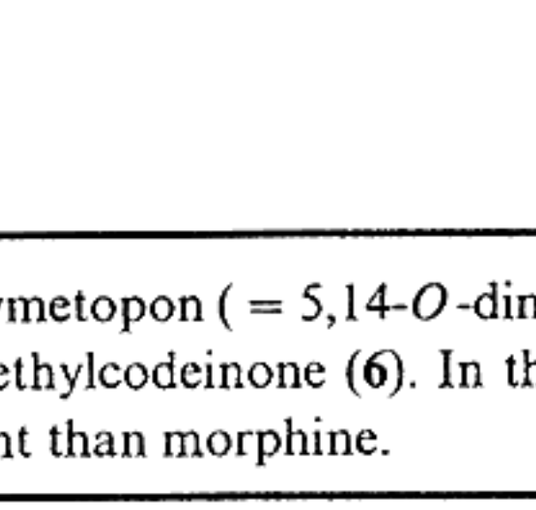
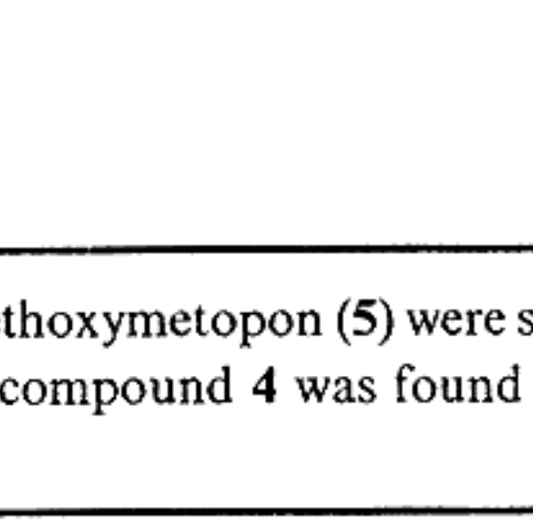
14-Methoxymetopon (= 5,14-*O*-dimethyloxymorphone; **4**) and 14-ethoxymetopon (**5**) were synthesized from 14-hydroxy-5-methylcodeinone (**6**). In the AcOH-writhing test in mice, compound **4** was found to be *ca.* 20000 times more potent than morphine.

Introduction. – 5-Methyloxymorphone (= 14-hydroxymetopon; **1**) was found to possess slightly less opioid-agonist properties than oxymorphone (**2**) [2]. When compared to the highly potent opioid agonist 14-*O*-methyloxymorphone (**3**) [3], compound **1**



1 $R^1 = R^3 = H$, $R^2 = CH_3$
2 $R^1 = R^2 = R^3 = H$ (oxymorphone)
3 $R^1 = CH_3$, $R^2 = R^3 = H$
4 $R^1 = R^2 = CH_3$, $R^3 = H$
5 $R^1 = C_2H_5$, $R^2 = CH_3$, $R^3 = H$
9 $R^1 = R^2 = R^3 = CH_3$
10 $R^1 = C_2H_5$, $R^2 = R^3 = CH_3$
12 $R^1 = C_2H_5$, $R^2 = R^3 = H$



6 $R^1 = H$, $R^2 = CH_3$
7 $R^1 = R^2 = CH_3$
8 $R^1 = C_2H_5$, $R^2 = CH_3$
11 $R^1 = CH_3$, $R^2 = H$

showed *ca.* 1/100th the antinociceptive potency in the AcOH-writhing test [2]. It was of interest if a 14-*O*-alkylation of **1** (to give compounds **4** and **5**) would enhance its opioid agonist properties to a similar extent as a 14-*O*-alkylation of oxymorphone into compound **3** could [3].

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[1]) Part 7: [1].

Chemistry. – Starting material was 14-hydroxy-5-methylcodeinone (**6**) which is readily available from 5-methylthebaine [2] [4]. Alkylation with either $(CH_3)_2SO_4$ or $(C_2H_5)_2SO_4$ gave the 14-alkoxy derivatives **7** and **8**, respectively. Catalytic hydrogenation (to afford **9** and **10**) followed by ether cleavage with 48% HBr solution yielded 14-methoxymetopon (**4**) and 14-ethoxymetopon (**5**), respectively.

Compound **4** was synthesized also by an alternative route. Ether cleavage of 14-methoxy-5-methylcodeinone (**7**) with 48% HBr solution afforded phenol **11** which was hydrogenated catalytically to give **4**.

Pharmacology. – Compounds **4**, **5**, and **11** have been evaluated for antinociceptive potency in the AcOH-writhing test in mice [2] [5] [6][2]). In this test, 14-methoxymetopon (**4**) was found to be *ca.* 20000 times more potent than morphine and 1500 times more potent than oxymorphone. 14-*O*-Methyloxymorphone (**3**), its analogue without 5-Me group, was 24 times less active.

14-Ethoxymetopone (**5**) showed less potency in the AcOH-writhing test – it was *ca.* 130 times less potent than its 14-MeO analogue **4**. The 7,8-didehydro derivative **11** was *ca.* 500 times less active than compound **4** (see the *Table*).

Table. *Antinociceptive Potencies of* **4, 5, 11,** *and Reference Drugs in the AcOH-Writhing Test in Mice* [2] [5] [6]

Compound	ED_{50}[a])	Compound	ED_{50}[a])
4·HBr	0.0199	**1**·HBr	52
5·HBr	2.7	**12**	1.23
11·HBr	9.2	Oxymorphone	31
3·HBr	0.48	Morphine sulfate	389

[a]) The ED_{50} is in μg/kg, s.c. (95% confidence interval).

Discussion and Conclusion. – The observation that a 14-MeO group in *N*-methylmorphinan-6-ones enhances opioid agonist properties [3] was confirmed. 14-Methoxymetopon (**4**) was found to be an extremely potent compound, with a potency that is *ca.* 2600 times higher compared to its 14-OH counterpart **1** in the AcOH-writhing test. Thus, a 14-*O*-methylation of 14-hydroxymetopon (= 5-methyloxymorphone; **1**) could significantly increase the opioid agonist properties.

14-Ethoxymetopon (**5**) was less potent than 14-methoxymetopon (**4**). A similar decrease in activity of a 14-EtO-substituted morphinans was found, when 14-*O*-ethyloxymorphone (**12**) was compared to 14-*O*-methyloxymorphone (**3**) [7]. Thus, the following order of increasing opioid agonist potency in 14-oxygenated *N*-methylmorphinan-6-ones was found: 14-OH < 14-EtO < 14-MeO.

We want to thank *Alkaloida, Chemical Factory*, H–4440 Tiszavasvári, Hungary, for the generous gift of thebaine and the Analytical Department of *F. Hoffmann-La Roche AG*, Basel, for elemental analyses.

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[2]) This test was performed for us at the *Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center*, Indianapolis, IN 46285, USA, through the courtesy of Dr. *J. D. Leander*.

Experimental Part

General. See [2].

(−)-7,8-Didehydro-4,5α-epoxy-3,14β-dimethoxy-5β,17-dimethylmorphinan-6-one (= 14β-Methoxy-5β-methylcodeinone; **7**). A soln. of *14-hydroxy-5-methylcodeinone* (**6**; 8.1 g, 24.74 mmol) in 60 ml anh. DMF was cooled to 0–5°. NaH (1.1 g, 45.8 mmol) was added under N_2, and the resulting mixture was stirred for 15 min. Then $(CH_3)_2SO_4$ (3.0 ml, 31.69 mmol) was added in one portion, and stirring was continued at 0–5° for 30 min. Excess NaH was destroyed carefully with small pieces of ice, then the mixture was poured on 250 ml ice/H_2O. After extractions with CH_2Cl_2 (3 × 80 ml), the combined org. layers were washed with H_2O (3 × 50 ml) and brine, dried, and evaporated to yield 8.4 g of a slightly yellow crystalline residue. Treatment with boiling EtOH gave 6.42 g (76%) of **7**. An anal. sample was prepared by recrystallization of a small portion from EtOH. M.p. 201–203°, $[\alpha]_D^{20} = -61.3$ ($c = 0.86$, $CHCl_3$). IR (KBr): 1670 (CO). ^{1}H-NMR ($CDCl_3$): 6.84 (*d*, $J = 10$, 1 olef. H); 6.52 (*s*, 2 arom. H); 6.05 (*d*, $J = 10$, 1 olef. H); 3.76 (*s*, CH_3O–C(3)); 3.28 (*s*, CH_3O–C(14)); 2.42 (*s*, CH_3N); 1.70 (*s*, CH_3–C(5)). Anal. calc. for $C_{20}H_{23}NO_4$ (341.41): C 70.36, H 6.79, N 4.10; found: C 70.11, H 7.08, N 3.95.

(−)-7,8-Didehydro-4,5α-epoxy-14β-ethoxy-3-methoxy-5β,17-dimethylmorphinan-6-one (= 14β-Ethoxy-5β-methylcodeinone; **8**) was prepared by the same procedure using $(C_2H_5)_2SO_4$. Recrystallization from EtOH gave 56% of **8**. M.p. 186–188°. $[\alpha]_D^{20} = -22.4$ ($c = 0.88$, $CHCl_3$). IR (KBr): 1670 (CO). ^{1}H-NMR ($CDCl_3$): 6.77 (*d*, $J = 10$, 1 olef. H); 6.40 (*s*, 2 arom. H); 6.02 (*d*, $J = 10$, 1 olef. H); 3.79 (*s*, CH_3O); 2.41 (*s*, CH_3N); 1.68 (*s*, CH_3–C(5)); 1.15 (*t*, $J = 6$, CH_3CH_2O). Anal. calc. for $C_{21}H_{25}NO_4$ (355.43): C 70.96, H 7.09, N 3.94; found: C 70.87, H 7.25, N 3.93.

(−)-4,5α-Epoxy-3,14β-dimethoxy-5β,17-dimethylmorphinan-6-one (= 14β-Methoxy-5β-methyloxycodone; **9**). A mixture of **7** (5.7 g, 16.69 mmol), 10% Pd/C (300 mg), and 150 ml of EtOH was hydrogenated at 20 psi and r.t. for 4 h. The catalyst was filtered off and the filtrate evaporated to give 5.58 g of a colorless crystalline solid which was treated with 10 ml boiling EtOH to yield 4.8 g of **9**. Another 470 mg were obtained from the mother liquor. Total yield 5.27 g (92%). A portion of this material was recrystallized for analysis. M.p. 187–190°. $[\alpha]_D^{20} = -139.0$ ($c = 0.82$, $CHCl_3$). IR (KBr): 1720 (CO). ^{1}H-NMR ($CDCl_3$): 6.54 (*s*, 2 arom. H); 3.80 (*s*, CH_3O–C(3)); 3.26 (*s*, CH_3O–C(14)); 2.36 (*s*, CH_3N); 1.57 (*s*, CH_3–C(5)). Anal. calc. for $C_{20}H_{25}NO_4$ (343.43): C 69.95, H 7.34, N 4.08; found: C 69.86, H 7.60, N 3.90.

(−)-4,5α-Epoxy-14β-ethoxy-3-methoxy-5β,17-dimethylmorphinan-6-one (= 14β-Ethoxy-5β-methyloxycodone; **10**) was prepared from **8** similary as described for **9**. Recrystallization from EtOH gave 83% of **10**. M.p. 165–167°. $[\alpha]_D^{20} = -163.3$ ($c = 1.13$, $CHCl_3$). IR (KBr): 1720 (CO). ^{1}H-NMR ($CDCl_3$): 6.54 (*s*, 2 arom. H); 3.83 (*s*, CH_3O); 2.32 (*s*, CH_3N); 1.61 (*s*, CH_3–C(5)); 1.24 (*t*, $J = 6$, CH_3CH_2O). Anal. calc. for $C_{21}H_{27}NO_4$ (357.45): C 70.56, H 7.61, N 3.92; found: C 70.38, H 7.72, N 3.92.

(−)-4,5α-Epoxy-3-hydroxy-14β-methoxy-5β,17-dimethylmorphinan-6-one Hydrobromide (= 14β-Methoxymetopon Hydrobromide; **4**·HBr). A soln. of **9** (800 mg, 2.33 mmol) in 48% HBr soln. (8 ml) was refluxed for 15 min and then evaporated to give a slightly pink foam. Crystallization from MeOH/Et_2O yielded 736 mg (77%) of **4**·HBr. Recrystallization of a small portion from MeOH/Et_2O afforded anal. pure material. M.p. 265–271°. $[\alpha]_D^{20} = -142.1$ ($c = 0.96$, DMF). IR (KBr): 3420, 3360 (OH, $^+$NH); 1720 (CO). ^{1}H-NMR ((D_6)DMSO): 9.30, 8.95 (2 br. *s*, OH, $^+$NH); 6.58 (*s*, 2 arom. H); 3.38 (*s*, CH_3O); 2.88 (*d*, $J = 4$, CH_3N^+); 1.49 (*s*, CH_3–C(5)). Anal. calc. for $C_{19}H_{23}NO_4$·HBr (410.31): C 55.62, H 5.90, N 3.41; found: C 55.37, H 5.80, N 3.36.

(−)-4,5α-Epoxy-14β-ethoxy-3-hydroxy-5β,17-dimethylmorphinan-6-one Hydrobromide (= 14β-Ethoxymetopon Hydrobromide; **5**·HBr) was prepared from **10** similarly as described for **4**·HBr. Recrystallization from acetone afforded 75% of **5**·HBr. M.p. > 325° (dec.) $[\alpha]_D^{20} = -105.9$ ($c = 0.83$, EtOH). IR (KBr): 3350, 3180 (OH, $^+$NH), 1720 (CO). ^{1}H-NMR ((D_6)DMSO): 8.56 (br. *s*, OH, $^+$NH); 6.55 (*s*, 2 arom. H); 2.95 (*d*, $J = 4$, CH_3N^+); 1.47 (*s*, CH_3–C(5)); 1.30 (*t*, $J = 6$, CH_3CH_2O). Anal. calc. for $C_{20}H_{25}NO_4$·HBr (424.34): C 56.61, H 6.18, N 3.30; found: C 56.68, H 6.23, N 3.26.

(−)-7,8-Didehydro-4,5α-epoxy-3-hydroxy-14β-methoxy-5β,17-dimethylmorphinan-6-one Hydrobromide (= 14β-Methoxy-5β-methylmorphinon Hydrobromide; **11**·HBr). A soln. of **7** (1.26 g, 3.7 mmol) in 48% HBr soln. (4 ml) was refluxed for 25 min and then evaporated. Crystallization of the residue (1.9 g of a brownish foam) from MeOH/Et_2O afforded 1.18 g (78%) of **11**·HBr. A small portion of this material was recrystallized from MeOH/Et_2O for analysis. M.p. 148–150°. $[\alpha]_D^{20} = -43.5°$ ($c = 0.75$, DMF). IR (KBr): 3420, 3360 (OH, $^+$NH); 1675 (CO). ^{1}H-NMR ((D_6)DMSO): 9.30 (br. *s*, OH, $^+$NH); 7.13 (*d*, $J = 10$, 1 olef. H); 6.54 (*s*, 2 arom. H); 6.25 (*d*, $J = 10$, 1 olef. H); 3.34 (*s*, CH_3O); 2,97 (*d*, $J = 4$, CH_3N^+); 1.54 (*s*, CH_3–C(5)). Anal. calc. for $C_{19}H_{21}NO_4$·HBr·0.2 H_2O (410.09): C 55.40, H 5.48, N 3.40; found: C 55.38, H 5.44, N 3.40.

Compound **11**·HBr (130 mg, 0.32 mmol) was hydrogenated as described for the formation of **9**. Yield: 80 mg (76%) of **4**·HBr. M.p., IR, and ^{1}H-NMR: identical with those of an authentic sample.

Pharmacology. See [2] [5] [6].

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