118. Structure-Activity Relationships of Oxygenated Morphinans. I. 4-Mono- and 3,4-Dimethoxy-*N*-methylmorphinans and -*N*-methylmorphinan-6-ones with Unusually High Antinociceptive Potency

Preliminary Communication

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Summary

The antinociceptive potency and receptor affinity of several optically active aromatic mono- and di-oxygenated *N*-methylmorphinans and *N*-methylmorphinan-6-ones, prepared from natural morphine, were determined. Thus, in order of antinociceptive potency, 4-methoxy-*N*-methylmorphinan-6-one ≈ 3,4-dimethoxy-*N*-methylmorphinan-6-one ≈ 3,4-dimethoxy-*N*-methylmorphinan > 4-methoxy-*N*-methylmorphinan ≈ 4-acetoxy-*N*-methylmorphinan-6-one > 4-acetoxy-*N*-methylmorphinan ≈ 4-hydroxy-*N*-methylmorphinan-6-one ≈ 4-hydroxy-*N*-methylmorphinan. The 4-hydroxy compounds were slightly less potent than morphine, and the 4-methoxy and 3,4-dimethoxy compounds were found to have three times the potency of morphine. 4-Methoxy-*N*-methylmorphinan-6-one showed an opiate receptor affinity one-third that of morphine; this is a remarkably high affinity for a non-phenolic compound.

Our observation that 3-deoxydihydromorphine and 3,6-dideoxydihydromorphine had considerable antinociceptive activity [1] led us to question the significance of the 4,5-epoxy O-atom. In order to discern whether a 4-oxygenated aromatic moiety would be sufficient alone, or in conjunction with other substituents, to produce morphine-like analgesia, we prepared many aromatic mono- and di-oxygenated morphinans, morphinanones, and their derivatives[4]).

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[4]) Details of this extensive investigation concerning oxygenated morphinans and morphinanones, and their *N*- and *O*-alkylated derivatives, will be reported elsewhere.

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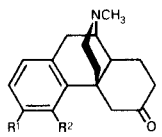
Considerable knowledge regarding the structure-activity relationship of aromatic oxygenated *N*-methylmorphinan derivatives was accumulated between 1950 and 1960 in the laboratories of *Hoffmann-La Roche* in Switzerland [2–5]. These efforts resulted already in 1949 in the discovery of (−)-3-hydroxy-*N*-methylmorphinan (**1**), introduced as a narcotic and orally effective analgesic under the generic name of levorphanol [6]. Its *O*-methyl ether **2** seemed to exhibit less attractive properties, although no details were given [2]. In the course of these investigations, 2- and 4-oxygenated morphinan derivatives were also prepared and are described in patent applications [7].

Our synthesis of (−)-4-hydroxy-*N*-methylmorphinan-6-one (**3**) from natural morphine [8–10][5]), and the conversion of a 3,4-catechol into its dimethyl ether **4** [11], afforded, after biological evaluation of these compounds, evidence that potent antinociceptives didn't need a phenolic hydroxy group in position 3 on the aromatic nucleus of the morphinan. We found that *O*-methylation of **3**, to give the ether **5**, produced a compound with an antinociceptive potency only slightly less than that of levorphanol (**1**) and three times the potency of morphine[6]). This suggested an extension of our investigation to a series of phenolic morphinan derivatives, 6-keto derivatives and their *O*-methyl ethers and related compounds. The results of this work shall now be summarized.

The *O*-methyl ether **5**[7]) was obtained from the phenol **3** by methylation with diazomethane or, preferably, phenyltrimethylammonium methoxide [12] [13] following standard procedures. Purification of the crude solid by chromatography

Scheme



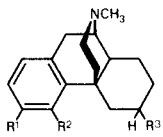
3 $R^1 = H, R^2 = OH$

5 $R^1 = H, R^2 = OCH_3$

6 $R^1 = H, R^2 = OCOCH_3$

11 $R^1 = R^2 = OCH_3$

12 $R^1 = OCH_3, R^2 = H$



1 $R^1 = OH, R^2 = R^3 = H$

2 $R^1 = OCH_3, R^2 = R^3 = H$

4 $R^1 = R^2 = OCH_3, R^3 = H$

7 $R^1 = R^3 = H, R^2 = OH$

8 $R^1 = R^3 = H, R^2 = OCOCH_3$

9 $R^1 = H, R^2 = OH, R^3 = \alpha\text{-OH}$

10 $R^1 = H, R^2 = OH, R^3 = \beta\text{-OH}$

13 $R^1 = R^3 = H, R^2 = OCH_3$

All compounds have been prepared from natural morphine, and the structures shown express their absolute configurations.

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5) The latter synthesis [10] describes the preparation of (±)-**3**.

6) Some of the data on the 4-hydroxy- and 4-methoxymorphinans and -morphinan-6-ones reported here were discussed by *F.-L.H.* at the American Society of Pharmacognosy, Purdue University, West Lafayette, Indiana, in August, 1979; by *M.D.R.* at the American Chemical Society Meeting in Houston, Texas, in March, 1980; and by *A.B.* at the University of Rochester, New York, and *Stanford Research Institute* in Palo Alto, California, in 1980, and at the University of Maryland, College Park, Maryland, and the *Merck Institute* in West Point, Pennsylvania, in January, 1981.

7) All new compounds were characterized by elemental analysis and show the expected spectroscopic features.

on alumina gave a 65% yield of **5**, m.p. 145–147° (benzene/petroleum ether), and $[\alpha]_D^{26} = -96.5°$ ($c = 1.02$, $CHCl_3$) [IR.[8]) (KBr): 1700 (C=O). – ^{1}H-NMR.[8]) ($CDCl_3$): 2.41 (*s*, 3 H, CH_3N); 3.82 (*s*, 3 H, CH_3O); 4.08 (*d*, $J = 13$, H–C(5)); 6.68 (*d*, $J = 7$, 1 H, ArH); 6.72 (*d*, $J = 7$, 1 H, ArH); 7.09 (*d*×*d*, $J = 7$, and 7, 1 H, ArH). – MS.: 285 (M^+)].

A mixture of **3**, acetic anhydride and pyridine gave the 4-acetoxy compound **6** in 65% yield, m.p. 96–97° (isopropyl ether), and $[\alpha]_D^{25} = -46.7°$ ($c = 1.126$, $CHCl_3$) [IR. (KBr): 1710 (C=O), 1765 (CH_3COO). – ^{1}H-NMR. ($CDCl_3$): 2.36 and 2.42 (2*s*, 3 H each, CH_3COO and CH_3N); 3.64 (*d*, $J = 14$, 1 H, H–C(5)); 6.84 (*d*, $J = 7$, 1 H, ArH); 6.99 (*d*, $J = 7$, 1 H, ArH); 7.11 (*d*×*d*, $J = 7$, and 7, 1 H, ArH). – MS.: 313 (M^+)].

The (–)-4-hydroxy-*N*-methylmorphinan (**7**) was prepared in 79% yield from the phenolic ketone **3** by a *Wolff-Kishner* reduction using hydrazine hydrate in triethylene glycol, m.p. 213–214.5° (ethyl acetate), and $[\alpha]_D^{25} = -35.4°$ ($c = 1.26$, CH_3OH) [IR. ($CHCl_3$): 3600, 3350 (OH). – ^{1}H-NMR. ($CDCl_3$): 2.39 (*s*, 3 H, CH_3N); 3.48 (*d*, $J = 13$, 1 H, H–C(5)); 6.42 (*d*, $J = 8$, 1 H, ArH); 6.65 (*d*, $J = 8$, 1 H, ArH); 6.95 (*d*×*d*, $J = 8$, and 8, 1 H, ArH). – MS.: 257 (M^+)[9])]. The hydrochloride salt of **7** had m.p. 282–284° (dec., ethanol/2-propanol), and $[\alpha]_D^{25} = -17.4°$ ($c = 1.00$, CH_3OH).

The (–)-4-acetoxy-*N*-methylmorphinan (**8**) was obtained in 69% yield as its hydrochloride salt by acetylation of **7** and treatment with HCl, m.p. 227–229°, and $[\alpha]_D^{26} = +11.4$ ($c = 1.28$, EtOH) [IR. (**8** · HCl; KBr): 1755 (C=O). – ^{1}H-NMR. (**8**; $CDCl_3$): 2.27 and 2.36 (2 *s*, 3 H each, CH_3COO and CH_3N); 6.76 (*d*, $J = 8$, 1 H, ArH); 7.10 (*m*, 2 H, ArH). – MS. (**8**; high resolution): 299.1875 (M^+) (calculated: 299.1879)].

According to the known procedure [12] [13], levorphanol (**1**) was methylated with phenyltrimethylammonium methoxide to give (–)-3-methoxy-*N*-methylmorphinan (**2**), m.p. 109–110° (hexane), and $[\alpha]_D^{26} = -52.6°$ ($c = 0.87$, EtOH) ([12]: m.p. 109–111° ($EtOH/H_2O$), $[\alpha]_D^{26} = -49.3°$ ($c = 1.5$, EtOH)).

A mixture of (–)-4,6α- and (–)-4,6β-dihydroxy-*N*-methylmorphinan (**9** and **10**) was prepared by sodium borohydride reduction of **3** in 10% aqueous 2-propanol. The mixture **9**/**10** was separated by chromatography on silica gel (elution with $CHCl_3$/MeOH/ammonium hydroxide 80:18:2), to give 50% of the 6α epimer **9**, m.p. 218–220° (acetone), and $[\alpha]_D^{20} = -27.8°$ ($c = 1.506$, MeOH) [IR. ($CHCl_3$): 3600, 3240 (OH). – ^{1}H-NMR. (CD_3OD): 2.34 (*s*, 3 H, CH_3N); 3.81 (*d*, $J = 14$, 1 H, H–C(5)); 4.06–4.14 (*m*, 1 H, C*H*OH); 6.52 (*d*, $J = 8$, 1 H, ArH); 6.61 (*d*, $J = 8$, 1 H, ArH); 6.89 (*d*×*d*, $J = 8$, and 8, 1 H, ArH). – MS.: 273 (M^+)]. The hydrobromide salt of **9** had m.p. 318–320° (dec., methanol/2-propanol), and $[\alpha]_D^{20} = -10.6°$ ($c = 1.13$, MeOH). The chromatography also gave the 6β-hydroxy isomer **10** in 24% yield, m.p. 132–134° ($CHCl_3$), and $[\alpha]_D^{20} = -63.7°$ ($c = 1.10$, MeOH) [IR. (KBr): [illegible] (OH). – ^{1}H-NMR. (CD_3OD): 2.44 (*s*, 3 H, CH_3N); 3.41–3.61 (*m*, 1 H, C*H*OH); 3.89

[8]) IR. spectra: $\tilde{\nu}_{max}$ in cm^{-1}. ^{1}H-NMR. spectra: at 100 MHz or 220 MHz; internal standard tetramethylsilane (= 0.0 ppm); *s* = singlet, *d* = doublet, *m* = multiplet, *J* = spin-spin coupling constant in Hz.

[9]) This material proved identical with a sample prepared by a different procedure and provided by Dr. *E. Mohacsi* from *Hoffmann-La Roche*, Nutley, New Jersey, U.S.A. [7].

(*d*, J=13, 1 H, H–C(5)); 6.65 (*d*, J=8, 1 H, ArH); 6.70 (*d*, J=8, 1 H, ArH); 7.01 (*d*×*d*, J=8, and 8, 1 H, ArH). – MS.: 273 (M^+)]. The hydrobromide salt of **10** had m.p. 194–196° (dec., methanol/ether), and $[\alpha]_D^{20} = -36.9°$ (c=0.96, MeOH).

The (–)-3,4-dimethoxy-*N*-methylmorphinan-6-one (**11**) was obtained in three steps from the morphine-derived 3,4-dihydroxy-*N*-formylmorphinan-6-one[4]). The latter was reacted with methyl *p*-toluenesulfonate to form an enol ether which, after acid hydrolysis of the *N*-formyl group and enol ether, and *N*-methylation led, after the usual work-up, to the desired 6-keto compound **11**, m.p. 117–118° (ether), and $[\alpha]_D^{26} = -90°$ (c=0.63, $CHCl_3$) [IR. (KBr): 1710 (C=O). – ^{1}H-NMR. ($CDCl_3$): 2.36 (*s*, 3 H, CH_3N); 3.77 (*s*, 3 H, CH_3O); 3.90 (*s*, 3 H, CH_3O); 6.73 (*m*, 2 H, ArH). – MS.: 315 (M^+)].

The synthesis of (–)-3,4-dimethoxy-*N*-methylmorphinan (**4**) was previously reported [11], as was the synthesis of (–)-3-methoxy-*N*-methylmorphinan-6-one[10]) (**12**) [14] [15].

Table. *Antinociceptive Activity and Receptor Binding Affinity of Selected Aromatic Oxygenated* (–)-N-*Methylmorphinans and* (–)-N-*Methylmorphinan-6-ones*

Compound	ED_{50}[a])	EC_{50}[b])		
		Absence of NaCl	Presence of NaCl	Presence/absence of NaCl
4-Hydroxy-*N*-methylmorphinan-6-one (**3**)[c])	4.4 (3.3–5.8)	54.5	120	2.2
4-Hydroxy-*N*-methylmorphinan (**7**)[d])	4.7 (3.5–6.8)	150	513	3.4
4-Methoxy-*N*-methylmorphinan-6-one (**5**)[c])	0.90 (0.71–1.1)	161	488	3.0
4-Methoxy-*N*-methylmorphinan (**13**)[e])	3.1 (2.2–4.2)	510	889	1.7
4-Acetoxy-*N*-methylmorphinan-6-one (**6**)[e])	3.0 (2.6–3.5)	112	645	5.8
4-Acetoxy-*N*-methylmorphinan (**8**)[c])	5.1 (3.6–6.8)	–		
3,4-Dimethoxy-*N*-methylmorphinan-6-one (**11**)[e])	1.1 (0.86–1.5)	–		
3,4-Dimethoxy-*N*-methylmorphinan (**4**)[c])	0.98 (0.59–1.6)	–		
4,6β-Dihydroxy-*N*-methylmorphinan (**10**)[d])	59.8 (44.9–79.9)	–		
4,6α-Dihydroxy-*N*-methylmorphinan (**9**)[e])	51.8 (37.3–71.7)	–		
3-Methoxy-*N*-methylmorphinan-6-one (**12**)[e])[10])	3.9 (3.2–4.9)	–		
Levorphanol (**1**) as tartrate	0.5 (0.2–0.7)	14	20	1.4
Levomethorphan (**2**)[e])	2.8 (1.8–4.4)	–		
Morphine sulfate	2.9 (2.5–3.3)	60	142	2.4

[a]) Antinociceptive activity determined by hot plate assay, sc injection [16–18]. The ED_{50}, the effective dose at which half the animals are effected, values are in μmol/kg. The parenthesized numbers are 95% standard error limits determined by computerized probit analysis. The salts were introduced in aqueous solution; the bases in an *Emulphor EL620* mixture[11]).

[b]) Binding affinity to rat brain homogenates. Values are in nmol[12]).

[c]) HCl salt. [d]) HBr salt. [e]) Base.

[10]) We thank Prof. *H. C. Beyerman*, from the Delft University of Technology in Delft, The Netherlands, for having provided us with a sample of optically active **12**.

[11]) The *Emulphor EL-620* was obtained through the courtesy of the *GAF Corp.*, New York, N.Y. A 10% solution of a 1:1 mixture of *Emulphor* (polyoxyethylated vegetable oil) and absolute ethanol, in 85% physiological saline solution, was used to dissolve, or suspend, the bases for sc injection.

[12]) Aliquots of a membrane preparation from rat cerebrum were incubated with ^{3}H-etorphine in the absence and presence of 150 mM NaCl, and in the presence of different concentrations of the drugs. Stereospecific, *i.e.*, opioid-receptor related, binding of etorphine is determined and the inhibitory potency of the drug is obtained from log-probit plots of data [19] [20].

It is noteworthy that methylation of the 3-hydroxy group in levorphanol (**1**) produces the less potent **2**, while a similar methylation of the 4-hydroxymorphinan **7** or 4-hydroxymorphinanone **3**, to give **13** or **5**, caused a remarkable increase in potency. It is very unusual to find methoxylated derivatives more potent than their comparable hydroxy relatives as antinociceptives. It suggests that structural changes at position 4 in the morphinan skeleton affect the antinociceptive potency, possibly for steric and/or electronic reasons, and that they could enhance the uptake of the drug into the central nervous system. The 6-keto group does not appear to greatly influence antinociceptive potency, as can be seen by comparing **3** with **7** and **5** with **13** (Table), but the keto group aids in the binding to the opiate receptor. The examined compounds appear to interact at morphine (μ) receptor sites from the rat brain homogenate[12]). The 4-methoxy-*N*-methylmorphinan-6-one (**5**) interacts remarkably effectively with that receptor. Most aromatic ethers interact only slightly (*e.g.* morphine has *ca.* 300 times greater affinity for the receptor than codeine).

The 4-acetyl group may hydrolyze quickly *in vivo*, thus showing antinociceptive potency comparable to its 4-hydroxy relative (**6** and **3** in the *Table*). The dimethoxy compounds **11** and **4**, also considerably more potent then their hydroxy relatives, seem more influenced in their *in vivo* activity by the 4-methoxy than by the 3-methoxy group. Conversion of the 6-keto group to an alcohol function (**9** and **10**) destroys activity. The decrease in antinociceptive activity caused by a 6-hydroxy group was previously noted with dihydromorphine, which is much less potent than its deoxy congener desomorphine.

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