Synthesis and Biological Evaluation of 14-Alkoxymorphinans

Part 15[1])

Novel δ Opioid Receptor Antagonists with High Affinity and Selectivity in the 14-Alkoxy-Substituted Indolomorphinan Series

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The indolomorphinans **4**–**7** were prepared from their corresponding morphinan-6-one derivatives **8**–**11** *via Fischer* indole synthesis. Compounds **4** and **5** exhibited higher antagonist potency at δ opioid receptors in the mouse *vas deferens* preparation than the reference drug HS 378 (**2**), while compounds **6** and **7** were less potent.

Introduction. – The rationale for the design of naltrindole (NTI; **1**; $C_3H_5CH_2$ = cyclopropylmethyl) by *Portoghese* and coworkers [2] was based on the 'message-address' concept [3][4]. This design strategy for nonpeptidic, δ-selective antagonists employed the naltrexone (= 17-(cyclopropylmethyl)-4,5α-epoxy-3,14-dihydroxymorphinan-6-one) pharmacophore for the message moiety and a key element in the leucine-enkephalin δ address [5][6]. The key element, which is believed to be the phenyl group of Phe^4 of leucine-enkephalin, was attached to the morphinan structure of naltrexone through a rigid spacer. The first target compound synthesized, NTI (**1**), contained a pyrrole spacer, because it was easily accessible from naltrexone by a *Fischer* indole synthesis. NTI is a δ opioid receptor antagonist with high δ affinity and good selectivity as found in bioassays. It displayed a relatively moderate antinociceptive potency in the writhing assay [7][8]. Interestingly, NTI was found to possess immunosuppressant effects while being less toxic (NTI does not show any cytotoxic effect) than cyclosporin [9–11]. Development of morphine tolerance and physical dependence is markedly suppressed by the administration of NTI before and during morphine treatment [12]. These effects are produced by NTI at dosages that do not block the antinociceptive effects due to interactions at μ receptors. NTI seems also to block the ability of cocaine to produce positive reinforcement in rats [13][14].

Aside from the demonstrated antinociceptive effect produced by agonist interaction at δ receptors [7], NTI has been employed to demonstrate that δ opioid receptors are involved in the antinociceptive effects of cholecystokinin octapeptide in mice [15] and in swimstress-induced antinociception in adult rats [16][17]. NTI was found to produce a

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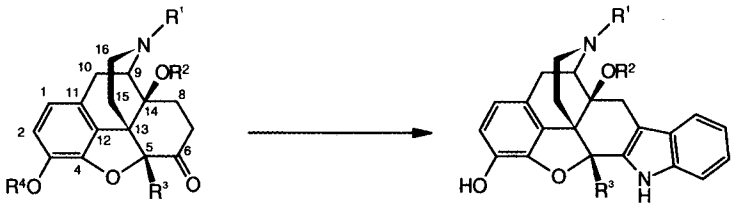
marked and long-lasting antitussive effect in mice and rats which was not antagonized by the irreversible μ antagonist β-FNA [18].

Introduction of a 14β-ethoxy and a 5β-methyl group onto the NTI molecule resulted in a pure opioid antagonist, HS 378 (**2**), with somewhat lower δ potency but much higher δ selectivity in the MVD due to very low μ and κ affinities [1]. Indole **2** was prepared by reacting the μ receptors preferring opioid antagonist 14-*O*-ethyl-5-methylnaltrexone (**3**) [19] with phenylhydrazine under conditions used for the *Fischer* indole synthesis.

Scheme



3 $R^1 = C_3H_5CH_2$, R^2 = Et, R^3 = Me, R^4 = H
8 $R^1 = C_3H_5CH_2$, R^2 = Me, $R^3 = R^4$ = H
9 $R^1 = C_3H_5CH_2$, R^2 = Et, $R^3 = R^4$ = H
10 $R^1 = C_3H_5CH_2$, $R^2 = R^3$ = Me, R^4 = H
11 $R^1 = H_2C{=}CHCH_2$, R^2 = Pr, R^3 = Me, R^4 = H
12 $R^1 = R^3 = R^4$ = Me, R^2 = H, 7,8-didehydro
13 $R^1 = R^3 = R^4$ = Me, $R^2 = H_2C{=}CHCH_2$, 7,8-didehydro
14 $R^1 = R^3 = R^4$ = Me, R^2 = Pr
15 $R^1 = CO_2CHClMe$, R^2 = Pr, $R^3 = R^4$ = Me
16 R^1 = H, R^2 = Pr, $R^3 = R^4$ = Me
17 $R^1 = H_2C{=}CHCH_2$, R^2 = Pr, $R^3 = R^4$ = Me

1 $R^1 = C_3H_5CH_2$, $R^2 = R^3$ = H
2 $R^1 = C_3H_5CH_2$, R^2 = Et, R^3 = Me
4 $R^1 = C_3H_5CH_2$, R^2 = Me, R^3 = H
5 $R^1 = C_3H_5CH_2$, R^2 = Et, R^3 = H
6 $R^1 = C_3H_5CH_2$, $R^2 = R^3$ = Me
7 $R^1 = H_2C{=}CHCH_2$, R^2 = Pr, R^3 = Me

In an attempt to improve on the δ affinity and/or selectivity of HS 378 (**2**) and to uncover structure-activity relationships in this series of compounds, we decided to prepare 5-Me-substituted and 5-unsubstituted indolomorphinans with different 14-alkoxy substituents.

Results and Discussion. – Here we report on the synthesis and biological evaluation of the novel 14-alkoxyindolomorphinans **4**–**7**. Compounds **4** and **5** were prepared from 14-*O*-methylnaltrexone (**8**) and 14-*O*-ethylnaltrexone (**9**) [20][21], respectively, compound **6** from 5,14-*O*-dimethylnaltrexone (**10**) [22], and compound **7** from 5-methyl-14-*O*-propylnaloxone (**11**) employing a *Fischer* indole synthesis.

Compound **11** was prepared starting from 14-hydroxy-5-methylcodeinone (**12**) [23] which is readily available from 5-methylthebaine [24][25] by oxidation with performic acid. 14-*O*-Allylation in DMF using NaH as a base afforded 14-(allyloxy)-5-methylcodeinone (**13**) and catalytic hydrogenation over Pd/C catalyst 7,8-dihydro-5-methyl-14-propoxycodeinone (**14**). *N*-Demethylation was accomplished with 1-chloroethyl carbonochloridate (= 1-chloroethyl chloroformate) [26] to give carbamate **15** as intermediate which was not further purified. Refluxing **15** in MeOH afforded *N*-demethylmorphinan **16** which was alkylated with allyl bromide in DMF in the pres-

ence of K_2CO_3 to give **17**. Ether cleavage with 48% HBr solution yielded 5-methyl-14-*O*-propylnaloxone (**11**).

Compounds **4**–**7** were evaluated in a bioassay (electrically stimulated mouse *vas deferens* preparation; MVD; *Table*) employing DPDPE (δ), DAMGO (μ), and U69593 (κ) as selective agonists. None of the compounds tested showed agonist potency in MVD, but all were effective antagonists in this tissue.

Table. *Antagonist* K_e *Values of Compounds* **4**–**7** *and HS 378* (**2**) *as Reference Drug, Determined in the Mouse* Vas deferens *Preparation* (MVD)

	K_e[a]) [nM]			Selectivity ratio	
	DPDPE (δ)	DAMGO (μ)	U69593 (κ)	μ/δ	κ/δ
4	0.056	11.09	61.25	198	1094
5	0.010	1.72	32.5	172	3250
6	0.200	54.25	>40[b])	271	>200
7	1.740	>75[c])	>75[c])	>43	>43
2 (HS 378)	0.144	88.26	>200[d])	613	1389

[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). [b]) There was no shift with the compound at κ receptors up to 40 nM. [c]) There was no shift with the compound at μ and κ receptors up to 75 nM. [d]) No K_e could be determined up to 200 nM.

Compounds **4** and **5** exhibited considerably higher antagonist potency at δ opioid receptors than HS 378 (**2**), while the μ/δ selectivity ratios of both were somewhat lower compared to HS 378 due to enhanced antagonist potency at μ receptors. The κ/δ selectivity ratio of compound **4** was higher than one thousand (similar to HS 378) and of compound **5** even higher than three thousand. The δ antagonist potency and selectivity of compound **6** was slightly weaker than that of HS 378 while the δ antagonist potency of **7** was *ca.* 10-fold weaker.

The results thus suggest that a 5-Me is not necessary for high δ opioid receptor antagonism, but a 5-Me group is obviously able to decrease antagonism at μ receptors. A 14-EtO group in indolomorphinans seems to be superior to both a 14-MeO group and a 14-PrO group.

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Experimental Part

General. M.p.: *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. Elemental analyses were performed at the Institute of Physical Chemistry of the University of Vienna.

(−)-17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14β-methoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride (= *7-(Cyclopropylmethyl)-5,6,7,8,8a,9,14,14b-octahydro-8a-methoxy-4,8-methanobenzofuro[2,3-a]-pyrido[4,3-b]carbazol-1-ol Hydrochloride*; **4** · HCl). A mixture of **8** [20][21] (100 mg, 0.28 mmol), phenylhydrazine hydrochloride (82 mg, 0.57 mmol), and AcOH (7 ml) was refluxed for 24 h (**4** · HCl started to precipitate after a few hours) and then cooled to r.t. yielding crystalline **4** · HCl (100 mg) which was recrystallized from MeOH/Et_2O:

87 mg (67%) of pure **4** · HCl. M.p. > 250° (dec.). $[\alpha]_D^{20} = -442.9$ ($c = 0.94$, MeOH). IR (KBr): 3405, 3397, 3281 (OH, NH, NH^+). ^{1}H-NMR ((D_6)DMSO): 11.37 (*s*, NH); 9.32 (*s*, OH); 8.98 (*s*, NH^+); 7.40–6.94 (*m*, 4 arom. H); 6.69 (*d*, $J = 8.1$, 1 arom. H); 6.61 (*d*, $J = 8.1$, 1 arom. H); 5.75 (*s*, H–C(5)); 3.15 (*s*, MeO). EI-MS: 428 (M^+). Anal. calc. for $C_{27}H_{28}N_2O_3 \cdot HCl \cdot 0.5\ H_2O$ (474.00): C 68.42, H 6.38, Cl 7.48, N 5.91; found: C 68.37, H 6.31, Cl 7.41, N 5.75.

(–)-17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14β-ethoxyindolo[2',3':6,7]morphinan-3-ol Hydrochloride (= *7-(Cyclopropylmethyl)-8a-ethoxy-5,6,7,8,8a,9,14,14b-octahyro-4,8-methanobenzofuro[2,3-a]pyrido[4,3-b]carbazol-1-ol Hydrochloride*; **5** · HCl). As described for **4** · HCl, with **9** [20][21] (200 mg, 0.54 mmol), phenylhydrazine hydrochloride (157 mg, 1.09 mmol), and AcOH (15 ml). The crystalline **5** · HCl (237 mg) was recrystallized from MeOH/Et_2O: 140 mg (54%) of pure **5** · HCl. M.p. > 250° (dec.): $[\alpha]_D^{20} = -430.7$ ($c = 0.97$, MeOH). IR (KBr): 3414, 3403, 3279 (OH, NH, NH^+). ^{1}H-NMR ((D_6)DMSO): 11.34 (*s*, NH); 9.30 (*s*, OH); 8.46 (*s*, NH^+); 7.39–6.93 (*m*, 4 arom. H); 6.69 (*d*, $J = 8.2$, 1 arom. H); 6.60 (*d*, $J = 8.2$, 1 arom. H); 5.80 (*s*, H–C(5)); 1.02 (*t*, $J = 7.0$, 3 H, $MeCH_2O$). EI-MS: 442 (M^+). Anal. calc. for $C_{28}H_{30}N_2O_3 \cdot HCl \cdot 0.6\ H_2O$ (489.83): C 68.66, H 6.63, Cl 7.24, N 5.72; found: C 68.53, H 6.33, Cl 7.51, N 5.66.

(–)-17-(Cyclopropylmethyl)-6,7-didehydro-4,5α-epoxy-14β-methoxy-5β-methylindolo[2',3':6,7]morphinan-3-ol Hydrochloride (= *7-(Cyclopropylmethyl)-5,6,7,8,8a,9,14,14b-octahydro-8a-methoxy-14b-methyl-4,8-methanobenzofuro[2,3-a]pyrido[4,3-b]carbazol-1-ol Hydrochloride*; **6** · HCl). A mixture of **10** [22] (620 mg, 1.68 mmol), phenylhydrazine hydrochloride (365 mg, 2.52 mmol), and AcOH (7 ml) was refluxed for 17 h, then poored on ice, alkalinized with conc. NH_4OH soln., and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layers were washed with H_2O (3 × 40 ml), dried (Na_2SO_4), and evaporated to give 1.11 g of a brown foam which was chromatographed (silica gel, CH_2Cl_2/MeOH 90:9 (*v*/*v*)) to yield a slightly yellow foam which was converted into the hydrochloride salt in the usual way: **6** · HCl (520 mg, 65%). An anal. sample was obtained by recrystallization of a small portion from MeOH. M.p. > 250° (dec.). $[\alpha]_D^{20} = -406.7$ ($c = 0.57$, MeOH). IR (KBr): 3515, 3220 (OH, NH, NH^+). ^{1}H-NMR ((D_6)DMSO): 11.30 (*s*, NH); 9.12 (*s*, OH); 8.93 (*s*, NH^+); 7.34 (*m*, 2 arom. H); 7.09 (*dd*, $J = 8.3, 8.3$, 1 arom. H); 6.95 (*dd*, $J = 8.3, 8.3$, 1 arom. H); 6.63 (*d*, $J = 8.1$, 1 arom. H); 6.56 (*d*, $J = 8.1$, 1 arom. H); 3.24 (*s*, MeO); 1.87 (*s*, Me). CI-MS: 443 ($[M + 1]^+$). Anal. calc. for $C_{28}H_{30}N_2O_3 \cdot HCl \cdot 0.7\ H_2O$ (491.67): C 68.41, H 6.64, Cl 7.21, N 5.70; found: C 68.52, H 6.86, Cl 7.48, N 5.65.

(–)-14β-(Allyloxy)-7,8-didehydro-4,5α-epoxy-3-methoxy-5β,17-dimethylmorphinan-6-one (= *14β-(Allyloxy)-5β-methylcodeinone*; **13**). NaH (1.88 g, 78.2 mmol; obtained from 3.4 g of a 60% NaH dispersion in oil by washings with petroleum ether) was added to a soln. of **12** [23] (6.4 g, 19.55 mmol) in anh. DMF (60 ml) under N_2 at 5° (bath temp.) while stirring. After 10 min, allyl bromide (3.17 ml, 36.6 mmol) was added and the resulting mixture stirred at 5° (bath temp.) for 2 h. Excess NaH was destroyed carefully by addition of small pieces of ice, and then the mixture was diluted with H_2O (150 ml) and extracted with CH_2Cl_2 (3 × 50 ml). The combined org. layers were washed with H_2O (3 × 100 ml) and brine (60 ml), dried (Na_2SO_4), and evaporated to yield a brownish oil (7.52 g) which was crystallized from EtOH (7 ml): 5.09 g (71%) of **13**, slightly yellow crystals. A small portion was recrystallized from EtOH to afford an anal. sample. M.p. 136–137°. $[\alpha]_D^{22} = -10.2$ ($c = 0.52$, MeOH). IR (KBr): 1664 (CO). ^{1}H-NMR ((D_6)DMSO): 6.78 (*d*, $J = 10.2$, 1 olef. H); 6.62 (*d*, $J = 8.2$, 1 arom. H); 6.54 (*d*, $J = 8.2$, 1 arom. H); 6.09 (*d*, $J = 10.2$, 1 olef. H); 5.87 (*m*, 1 olef. H); 5.15 (*m*, 2 olef. H); 3.79 (*s*, MeO); 2.44 (*s*, MeN); 1.71 (*s*, Me). CI-MS: 368 ($[M + 1]^+$). Anal. calc. for $C_{22}H_{25}NO_4$ (367.45): C 71.91, H 6.86, N 3.81; found: C 71.69, H 7.03, N 3.75.

(–)-4,5α-Epoxy-3-methoxy-5β,17-dimethyl-14β-propoxymorphinan-6-one (= *7,8-Dihydro-5β-methyl-14β-propoxycodeinone*; **14**). A mixture of **13** (6.51 g, 17.7 mmol), 10% Pd/C (325 mg) and EtOH (170 ml) was hydrogenated at 30 psi and r.t. for 2 h. The catalyst was filtered off and the filtrate evaporated. The colorless oil (6.49 g) was crystallized from little EtOH: 6.12 g (93%) of **14**. M.p. 102–104°. $[\alpha]_D^{22} = -143.5$ ($c = 0.52$, MeOH). IR (KBr): 1718 (CO). ^{1}H-NMR ((D_6)DMSO): 6.65 (*d*, $J = 8.1$, 1 arom. H); 6.56 (*d*, $J = 8.1$, 1 arom. H); 3.76 (*s*, MeO); 2.35 (*s*, MeN); 1.61 (*s*, Me); 1.00 (*t*, $J = 7$, $MeCH_2CH_2O$). CI-MS: 372 ($[M + 1]^+$). Anal. calc. for $C_{22}H_{29}NO_4 \cdot 0.2$ EtOH (380.69): C 70.67, H 8.00, N 3.68; found: C 70.64, H 7.72, N 3.69.

(–)-4,5α-Epoxy-3-methoxy-5β-methyl-14β-propoxymorphinan-6-one Hydrochloride (**16** · HCl). A mixture of **14** (5.8 g, 15.6 mmol), $KHCO_3$ (7.8 g, 78.1 mmol), 1-chloroethyl carbonochloridate (10.27 ml, 93.6 mmol), and EtOH-free $ClCH_2CH_2Cl$ (80 ml) was stirred under reflux for 17 h. The inorg. material was filtered off and the filtrate evaporated to give **15** (9.49 g) as a brownish oil which was not further purified and characterized. This oil was dissolved in MeOH (20 ml) and refluxed for 1 h. Evaporation afforded 7.08 g of a slightly brown foam which was crystallized from MeOH/Et_2O: 5.0 g (81%) of **16** · HCl. An anal. sample was obtained upon recrystallization of a small portion from MeOH/Et_2O. M.p. 178–180°. $[\alpha]_D^{22} = -98.5$ ($c = 0.59$, MeOH). IR (KBr): 1725 (CO). ^{1}H-NMR ((D_6)DMSO): 10.11, 8.15 (2 br. *s*, NH_2^+); 6.83 (*d*, $J = 8.2$, 1 arom. H); 6.74 (*d*, $J = 8.2$, 1 arom. H); 3.78 (*s*, MeO); 1.48 (*s*, Me); 0.95 (*t*, $J = 7.4$, $MeCH_2CH_2O$). EI-MS: 357 (M^+). Anal. calc. for

$C_{21}H_{27}NO_4 \cdot HCl \cdot 0.6\ MeOH$ (413.14): C 62.80, H 7.42, Cl 8.58, N 3.39; found: C 62.66, H 7.34, Cl 8.98, N 3.40.

(–)-17-Allyl-4,5α-epoxy-3-methoxy-5β-methyl-14β-propoxymorphinan-6-one (**17**). A mixture of **16** · HCl (1.45 g, 3.68 mmol), K_2CO_3 (2.87 g, 20.8 mmol), allyl bromide (0.36 ml, 4.06 mmol), and anh. DMF was stirred at 80° (bath temp.) for 1.5 h. The inorg. material was filtered off and the filtrate evaporated to give 1.7 g of a yellowish oil which was partitioned between CH_2Cl_2 (30 ml) and H_2O (20 ml). The org. layer was washed with H_2O (3 × 20 ml) and brine (15 ml), dried (Na_2SO_4), and evaporated to give 1.38 g of an oily residue which was crystallized from EtOH: 1.28 g (88%) of **17**. A small portion was recrystallized from EtOH to afford an anal. sample. M.p. 122–124°. $[\alpha]_D^{22} = -174.7$ ($c = 1.01$, EtOH). IR (KBr): 1721 (CO). ^{1}H-NMR ($CDCl_3$): 6.63 (*d*, $J = 8.3$, 1 arom. H); 6.55 (*d*, $J = 8.3$, 1 arom. H); 5.79 (*m*, 1 olef. H); 5.13 (*m*, 2 olef. H); 3.84 (*s*, MeO); 1.60 (*s*, Me); 1.00 (*t*, $J = 7.4$, $MeCH_2CH_2O$). EI-MS: 397 (M^+). Anal. calc. for $C_{24}H_{31}NO_4$ (397.52): C 72.52, H 7.86, N 3.52; found: C 72.14, H 7.76, N 3.44.

(–)-17-Allyl-4,5α-epoxy-3-hydroxy-5β-methyl-14β-propoxymorphinan-6-one Hydrobromide (**11** · HBr). A soln. of **17** (880 mg, 2.21 mmol) in 48% HBr soln. (4 ml) was refluxed for 20 min and then evaporated. The residue was dissolved in MeOH (2 ml) and again evaporated to give 1.31 g of a gray foam which was crystallized from MeOH/Et_2O: 771 mg (75%) of **11** · HBr. An anal. sample was obtained upon recrystallization of a small portion. M.p. 244–247°. $[\alpha]_D^{22} = -109.9$ ($c = 1.01$, MeOH). IR (KBr): 3441, 3332 (OH, NH^+), 1725 (CO). ^{1}H-NMR ((D_6)DMSO): 9.42, 8.49 (2*s*, OH, NH^+); 6.68 (*d*, $J = 8.2$, 1 arom. H); 6.62 (*d*, $J = 8.2$, 1 arom. H); 5.92 (*m*, 1 olef. H); 5.67 (*m*, 2 olef. H); 1.49 (*s*, Me); 0.96 (*t*, $J = 7.4$, $MeCH_2CH_2O$). EI-MS: 383 (M^+). Anal. calc. for $C_{23}H_{29}NO_4 \cdot HBr \cdot 1.1\ H_2O$ (484.21): C 57.05, H 6.70, N 2.89; found: C 56.86, H 6.93, N 2.79.

(–)-17-Allyl-6,7-didehydro-4,5α-epoxy-5β-methyl-14β-propoxyindolo[2',3':6,7]morphinan-3-ol Methanesulfonate (= *5,6,7,8,8a,9,14,14b-Octahydro-14b-methyl-7-(prop-2-enyl)-8a-propoxy-4,8-methanobenzofuro[2,3-a]-pyrido[4,3-b]carbazol-1-ol Methanesulfonate*; **7** · $MeSO_3H$). A mixture of **11** · HBr (300 mg, 0.65 mmol), phenylhydrazine hydrochloride (187 mg, 1.29 mmol), and AcOH (30 ml) was refluxed for 8 h, evaporated, alkalinized with conc. NH_4OH soln., and extracted with CH_2Cl_2 (3 × 30 ml). The combined org. layers were washed with H_2O (3 × 20 ml) and brine (20 ml), dried (Na_2SO_4), and evaporated to give 325 mg of a slightly brown foam which was converted into the methanesulfonate in the usual way: 264 mg (74%) of **7** · $MeSO_3H$ (MeOH/Et_2O). M.p. > 256° (dec.). $[\alpha]_D^{24} = -316.7$ ($c = 1.03$, MeOH). IR (KBr): 3368, 3146, 3027 (OH, NH, NH^+). ^{1}H-NMR ((D_6)DMSO): 11.29 (*s*, NH); 9.16 (*s*, OH); 8.45 (*s*, NH^+); 7.34–6.91 (*m*, 4 arom. H); 6.69 (*d*, $J = 8.1$, 1 arom. H); 6.52 (*d*, $J = 8.1$, 1 arom. H); 5.95 (*m*, 1 olef. H); 5.75 (*s*, H–C(5)); 5.64 (*m*, 2 olef. H); 2.32 (*s*, $MeSO_3^-$); 0.55 (*t*, $J = 7.3$, $MeCH_2CH_2O$). FAB-MS: 457 ($[M + 1]^+$). Anal. calc. for $C_{29}H_{32}N_2O_3 \cdot MeSO_3H \cdot 0.5\ H_2O$ (561.68): C 64.15, H 4.64, N 4.99, S 5.71; found: C 64.08, H 6.87, N 5.09, S 5.87.

Biological Evaluation. The electrically stimulated mouse *vas deferens* preparation (MVD) was performed as previously described [27].

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