76. A Simple and Efficient Method for the Preparation of Binaltrorphimine and Derivatives and Determination of their κ Opioid Antagonist Selectivity

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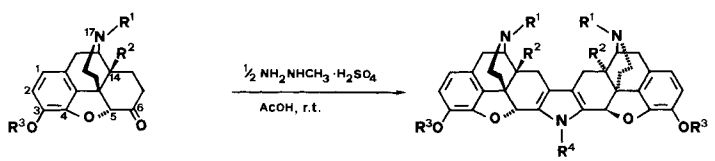
(20.II.89)

The bimorphinans **1** (binaltrorphimine), **3**, and **7** have been prepared by treatment of the parent morphinan-6-ones naltrexone (**5**), naloxone (**4**), and dihydrocodeinone (**6**), respectively, with *N*-methylhydrazine sulfate in AcOH at room temperature. Compound **3** showed opioid antagonist potency and selectivity for κ receptors which were somewhat lower in comparison to **1**.

The bimorphinans binaltrorphimine (**1**) and norbinaltrorphimine (**2**) were the first opioid antagonists with high selectivity for κ opioid receptors and are widely used as pharmacological tools [1–4]. In consideration of these desirable pharmacological features, we decided to prepare the *N,N'*-diallyl analogue **3** of binaltrorphimine (**1**) by the method described by *Portoghese et al.* [1] for the synthesis of **1**. The synthesis of **1** had been accomplished by heating naltrexone hydrochloride (**5** · HCl) and *N*-methylhydrazine hydrochloride in DMF on a steam bath for 2 h. Our attempts to prepare compound **3** by this procedure failed, thus we sought for an efficient method for the preparation of this naloxone-derived bimorphinan.

Chemistry. – With dihydrocodeinone (**6**) as model substance, we found that the formation of the bimorphinan **7** proceeded smoothly in AcOH at room temperature using *N*-methylhydrazine sulfate as reagent. The naloxone-derived bimorphinan **3** and binaltrorphimine (**1**) were prepared similarly from naloxone (**4**) and naltrexone (**5**), respectively *(Scheme)*. This procedure we found for the preparation of bimorphinans having a *N*-methyl group at the pyrrol moiety takes place under milder conditions and gives better results in comparison to the known procedure [1].



4 $R^1 = CH_2CH{=}CH_2$, R^2 = OH, R^3 = H (naloxone)
5 R^1 = cyclopropylmethyl, R^2 = OH, R^3 = H (naltrexone)
6 $R^1 = R^3 = CH_3$, R^2 = H

1 R^1 = cyclopropylmethyl, R^2 = OH, R^3 = H, $R^4 = CH_3$ (binaltrorphimine)
2 R^1 = cyclopropylmethyl, R^2 = OH, $R^3 = R^4$ = H (norbinaltrorphimine)
3 $R^1 = CH_2CH{=}CH_2$, R^2 = OH, R^3 = H, $R^4 = CH_3$
7 $R^1 = R^3 = R^4 = CH_3$, R^2 = H

Pharmacology. – Compound **3** was evaluated *in vitro* for opioid antagonist properties in the isolated guinea-pig ileal longitudinal muscle preparation (GPI) and in the mouse *vas deferens* preparation (MVD). In the GPI, the antagonist effect was tested against normorphine (μ-selective agonist) and ethylketocyclazocine (κ-selective agonist). In the MVD, normorphine, ethylketocyclazocine, and [D-Ala^2,D-Leu^5]enkephalin (acts as a selective δ agonist in the MVD because this preparation has a large δ receptor reserve) were used as ligands *(Table)*.

Table. *Potencies of* **3**, *Binaltrorphimine* (**1**), *and Norbinaltrorphimine* (**2**) *in the MVD and GPI*

		Ke[a]) [n*M*]			Selectivity ratio	
		ethylketocyclazocine (κ)	normophine (μ)	[D-Ala^2,D-Leu^5]enkephalin (δ)	μ/κ	δ/κ
3	MVD	0.87	35.3	6.1	41	6
	GPI	0.11	5.7	–	52	–
1	MVD	0.22	13.2	3.1	60	14
	GPI	0.04	4.6	–	115	–
2	MVD	0.05	63	22	1260	440
	GPI	0.02	27	–	1350	–

[a]) *Ke* = [antagonist]/*DR-1*, where *DR* is the dose ratio (*i.e.* ratio of equiactive concentrations of the test agonist in the presence and absence of the antagonist).

In the MVD and GPI, compound **3** showed opioid antagonist potency and selectivity for κ receptors. Its antagonist potency and κ selectivity was somewhat inferior to those of binaltrorphimine (**1**). Compound **3** did not show, like **1**, any agonist activity.

Experimental Part

General. Column chromatography: basic alumina (70–230 mesh ASTM) from *Merck*. Prep. TLC: silica-gel plates (*Kieselgel 60 F*; 2 mm) from *Merck*; $CHCl_3$/MeOH/NH_4OH 90:9:1. M.p.: *Kofler* melting point microscope; uncorrected. IR spectra (in cm^{-1}): *Beckman AccuLab 2* apparatus. ^{1}H-NMR spectra: *Bruker AM 300* spectrometer. CI-MS: *Finnigan MAT 44S* apparatus and *VG-7035* mass spectrometer.

6,6',7,7'-Tetradehydro-4,5:4',5'-diepoxy-3,3'-dimethoxy-17,17'-dimethyl-6,6'-(methylimino)-7,7'-bimorphinan (**7**). A soln. of carefully dried **6** (1.5 g, 5.0 mmol) and *N*-methylhydrazine sulfate (360 mg, 2.5 mmol) in AcOH (8 ml) was stirred under N_2 at r.t. for 3 h (after *ca.* 30 min, a colorless precipitation began to separate). The mixture was alkalinized with conc. NH_4OH soln., after addition of 5 ml of ice/H_2O, and extracted with CH_2Cl_2 (15 ml) and the org. layer dried and evaporated: 1.4 g of a slightly brown oily residue. Crystallization from MeOH afforded 870 mg (62%) of **7**. Recrystallization of a small portion of this material gave an anal. sample. M.p. > 300° (dec.). ^{1}H-NMR ($CDCl_3$): 6.65 (*d*, *J* = 8, 2 arom. H); 6.58 (*d*, *J* = 8, 2 arom. H); 5.46 (*s*, H–C(5), H–C(5')); 3.82 (*s*, 2 CH_3O); 3.76 (*s*, CH_3N); 2.40 (*s*, CH_3–N(17), CH_3–N(17')). CI-MS: 592 ([*M* + 1]$^+$). Anal. calc. for $C_{37}H_{41}N_3O_4 \cdot 0.3$ MeOH (601.36): C 74.50, H 7.07, N 6.99; found: C 74.53, H 7.02, N 6.99.

17,17'-Diallyl-6,6',7,7'-tetradehydro-4,5:4',5'-diepoxy-6,6'-(methylimino)-[7,7'-bimorphinan]-3,3',14,14'-tetrol (**3**). A soln. of carefully dried naloxone (**4**; 2.5 g, 7.6 mmol) and *N*-methylhydrazine sulfate (550 mg, 3.82 mmol) in AcOH (8 ml) was stirred under N_2 at r.t. for 20 h (after *ca.* 3 h, an orange-red precipitation began to separate). The mixture was alkalinized with conc. NH_4OH soln., after addition of ice, and extracted with CH_2Cl_2/MeOH 2:1 (2 × 15 ml), the org. layer dried and evaporated, and the brown oil (2.35 g) chromatographed with CH_2Cl_2/MeOH 95:5 (column 20 × 4 cm; alumina, basic, grade IV): 2.15 g (86%) of **3** as a yellowish foam. For analysis, a portion of this material was further purified by prep. TLC; **3** as slightly yellow powder. M.p. > 300° (dec.). IR (KBr): 3360 and 3350 (OH). ^{1}H-NMR ($CDCl_3$): 6.59 (*d*, *J* = 8, 2 arom. H); 6.48 (*d*, *J* = 8, 2 arom. H); 5.80 (*m*, 2 olef. H); 5.49

(*s*, H–C(5), H–C(5′)); 5.17 (*m*, 4 olef. H); 3.77 (*s*, CH_3N). CI-MS: 648 ($M^+ + 1$). Anal. calc. for $C_{39}H_{41}N_3O_6 \cdot 2\ H_2O$ (683.77): C 68.50, H 6.63, N 6.15; found: C 68.78, H 6.37, N 6.27.

17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(methylimino)-[7,7′-bimorphinan]-3,3′,14,14′-tetrol (**1**) [1]. A soln. of carefully dried naltrexone (**5**; 395 mg, 1.16 mmol) and *N*-methylhydrazine sulfate (92 mg, 0.64 mmol) in AcOH (4 ml) was stirred at r.t. under N_2 for 20 h (after *ca.* 3 h a red-orange precipitation began to separate). After addition of 20 ml of ice/H_2O and 20 ml of conc. NH_4OH soln. and extraction with $CHCl_3$/EtOH 2:1 (2 × 15 ml), the combined org. layers were dried and evaporated: 350 mg of a slightly brown glassy solid which was crystallized from MeOH to yield 298 mg (76%) of **1** as slightly yellow crystals. M.p. > 260° (dec., [1]: > 260° (dec.)). ^{1}H-NMR ($CDCl_3$): 6.58 (*d*, $J = 8$, 2 arom. H); 6.47 (*d*, $J = 8$, 2 arom. H); 5.52 (*s*, H–C(5), H–C(5′)); 3.79 (*s*, CH_3N). CI-MS: 676 ($[M + 1]^+$). Anal. calc. for $C_{41}H_{45}N_3O_6 \cdot$ MeOH (707.87): C 71.26, H 6.98, N 5.94; found: C 71.12, H 6.73, N 6.19.

Pharmacology. See [5].

We want to thank Prof. Dr. *Zoltan Dinya* (Department of Organic Chemistry, University of Debrecen, Hungary) and Prof. Dr. *K.-H. Ongania* (Institute of Organic and Pharmaceutical Chemistry, University of Innsbruck) for recording the mass spectra and *H.-P. Kählig* for performing the NMR spectra. We further thank the Analytical Department of *F. Hoffmann-La Roche & Co. AG*, Basel, for elemental analyses.

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