dissolved separately in methanol at 60 °C (400 + 400 mL) and mixed, the solution was cooled, and the resulting solid was collected by filtration. The solid (27.3 g) was put aside, and then the mother liquors were concentrated to 170 mL, cooled, and filtered to remove further solid, which was discarded. The resulting mother liquors were further concentrated to 120 mL, cooled, filtered (the solid discarded), and then evaporated to dryness. The resulting solid (23 g) was partitioned between dichloromethane and aqueous (20%) potassium hydroxide solution; the dichloromethane layer was evaporated to give crude parent amine, which was distilled in vacuo to yield the pure (+) enantiomer of the diamine as a colorless liquid: bp 116–119 °C (13 mm); 3.1 g (17 mmol, 19%); $[\alpha]^{20}_D$ (CH_2Cl_2) +91.5°.

A portion of the solid collected from the first crystallization was recrystallized three times from methanol, and the parent amine was regenerated by partitioning between dichloromethane and aqueous (20%) potassium hydroxide solution as described above to yield the pure (-) enantiomer of the diamine: bp 116–119 °C (13 mm); 2.9 g (16 mmol, 18%); $[\alpha]^{20}_D$ (CH_2Cl_2) -92.3°.

Both enantiomers of the diamine were separately acylated with 4-benzo[*b*]thiopheneacetyl chloride as described in method A. The (+) amine (0.20 g, 1.1 mmol) yielded compound **37** (0.27 g, 0.69 mmol, 63%) (the (-) enantiomer of **15**), $[\alpha]^{20}_D$ (CH_2Cl_2) -27°, while the (-) amine (0.20 g, 1.1 mmol) yielded **38** (0.30 g, 0.77 mmol, 70%) (the (+) enantiomer of **15**), $[\alpha]^{20}_D$ (CH_2Cl_2) +30°. Similarly, acylation with 4-benzo[*b*]furanacetyl chloride yielded, from the (+) amine (0.60 g, 3.3 mmol), **39** (0.85 g, 2.0 mmol, 61%) (the (-) enantiomer of **14**), $[\alpha]^{20}_D$ (CH_2Cl_2) -35°, and from the (-) amine (0.40 g, 22 mmol), **40** (0.59 g, 1.6 mmol, 73%) (the (+) enantiomer of **14**), $[\alpha]^{20}_D$ (CH_2Cl_2) +42.5°.

The enantiomeric purity of both of the separated amine enantiomers, **37–40**, were all assayed by using the chiral solvating agent method of Pirkle and Hoover.[29] ^1H NMR spectra of equimolar solutions of the compound and (*R*)-(-)-2,2,2-trifluoro-1-(9-anthranyl)ethanol in $CDCl_3$ solution were obtained at 300 mHz. When racemic compounds were used, each resonance in the normal spectrum split into two components, due to the difference between the solvent shifts imparted to each enantiomer by the chiral solvating agent. The most clearly resolved differences were for the two doublets of the AB quartet to Ar CH_2 ($\Delta\delta$ between enantiomers 0.037 ppm for the lower field doublet and 0.053 ppm for the higher field doublet), and for the N*Me* singlet ($\Delta\delta$ between enantiomers, 0.103 ppm). When compounds **37–40** were tested, signals corresponding to only one enantiomer were observed, the opposite enantiomer therefore being absent within the confidence limits of the experiment (>98%) in each case.

Acknowledgment. The X-ray crystallographic structural data for compound **37** was kindly provided by Dr. D. J. Williams (Imperial College, London). Determination of the optical purity of compounds and conformational analysis by NMR was performed by Dr. D. Neuhaus. Elemental analyses were determined by Dr. F. A. McKellar, the Analytical Chemistry Section, Parke-Davis/Warner-Lambert Pharmaceutical Research, Ann Arbor, Michigan, and by C. H. N. Analysis Limited, Leicester, U.K. We thank S. Turner for technical assistance.

Supplementary Material Available: Crystal data for **27** and tables listing bond lengths and angles, atom coordinates and temperature factors, anisotropic temperature factors, and hydrogen coordinates and temperature factors (9 pages). Ordering information is given on any current masthead page.

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Binaltorphimine-Related Bivalent Ligands and Their κ Opioid Receptor Antagonist Selectivity

P. S. Portoghese,*† H. Nagase,† A. W. Lipkowski,† D. L. Larson,† and A. E. Takemori‡

Department of Medicinal Chemistry, College of Pharmacy, and Department of Pharmacology, School of Medicine, University of Minnesota, Minneapolis, Minnesota 55455. *Received September 24, 1987*

In an effort to develop selective antagonists for κ opioid receptors, bivalent ligands that contain opioid antagonist pharmacophores derived from naltrexone or other morphinans were synthesized and tested on the guinea pig ileum (GPI) and mouse vas deferens (MVD) preparations. The minimum requirements for κ selectivity are at least one free phenolic OH group and one *N*-cyclopropyl or *N*-allyl substituent. Several compounds (**3**, **8**, **10**) with κ selectivity as good as or better than norbinaltorphimine (nor-BNI, **2**) were discovered. The structure–activity relationship revealed that the pyrrole ring functions strictly as a spacer and does not contribute to κ selectivity. The pharmacologic data suggest that only one antagonist pharmacophore may be required for κ selectivity and that the other morphinan portion of the molecule confers selectivity by interacting with a unique subsite proximal to the antagonist pharmacophore recognition locus.

The existence of receptor subpopulations among different receptor classes is now generally recognized. For this reason the advances in many areas of medicinal chemistry and pharmacology depend greatly on highly selective ligands as tools. Since cross-recognition of multiple receptor populations by a ligand may lead to ambiguities in the analysis of structure–activity relationship studies, it is particularly important that highly selective tools are available for this purpose. This is particularly relevant to opioid receptors, as there are at least three major receptor types (μ, κ, δ) in this class.[1]

The opioid antagonists naloxone and naltrexone have been employed extensively as tools in opioid research.[2,3] However, while useful in determining the possible involvement of an opioid mechanism, these antagonists are insufficiently selective to sort out actions mediated by subpopulations of opioid receptors.

In an effort to design highly selective opioid antagonists, we have employed the bivalent ligand approach using a naltrexone-derived antagonist pharmacophore.[4] The term "bivalent ligand" has been given to molecules that contain two recognition units linked through a spacer.[5] The basic assumption was that enhanced potency and selectivity can

† Department of Medicinal Chemistry.
‡ Department of Pharmacology.

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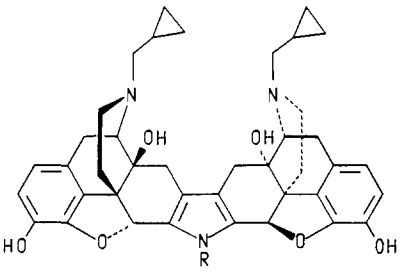
be conferred by the simultaneous occupation of proximal recognition sites by both units of a single bivalent ligand. We have found that the effectiveness with which two pharmacophores bridge proximal recognition sites depends on the length and conformational flexibility of the spacer,[6,7] and this was the basis for the design of the first highly selective κ opioid receptor antagonists, binaltorphimine (1, BNI) and norbinaltorphimine (2, nor-BNI).[8,9] Here we

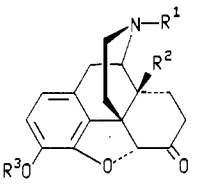


1: R = Me
2: R = H

explore the structure–activity relationship of this series of bimorphinans 1–11 in an effort to optimize κ opioid receptor selectivity.

Design Rationale and Chemistry. Since it has been reported[5–7] that the potency and selectivity of opioid antagonist bivalent ligands is a function of the length and flexibility of the spacer, an effort was made to design bivalent ligands with rigid spacers. This was based on the idea that immobilization of the antagonist pharmacophores in an orientation that permits binding to a unique site that is proximal to the opioid receptor would confer high selectivity by increasing the affinity of the ligand to a specific opioid receptor type.

Naltrexone (13) or naloxone (14) were selected as the pharmacophores to be modified because they are pure antagonists at all three receptor types and can be modified in the C ring due to the ketone group. Agonists 15–17 also



13: $R^1 = CH_2CH(CH_2)_2$; R^2 = OH; R^3 = H
14: $R^1 = CH_2CH{=}CH_2$; R^2 = OH; R^3 = H
15: $R^1 = CH_3$; R^2 = OH; R^3 = H
16: $R^1 = CH_3$; R^2 = H; R^3 = H
17: $R^1 = CH_3$; R^2 = H; $R^3 = CH_3$

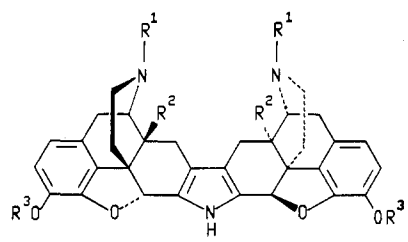
were incorporated into bivalent ligands to evaluate the *N*-methyl group on antagonist activity. The choice of pyrrole as a spacer was based on its synthetic accessibility via the Piloty synthesis[10] and on the ability of a flat heterocyclic ring to restrict conformational mobility by virtue of fusion at positions C-6 and C-7 of the morphinan structure. Peripheral modifications of the basic structure 2 were made in order to evaluate the contribution of different functional groups to κ opioid receptor antagonist potency and selectivity.

Nor-BNI (2) and related bivalent ligands 3–6 were synthesized by heating a DMF solution of the corresponding ketones 13–17 with *N*-aminosuccinimide hydrochloride or with hydrazine hydrochloride.[11] BNI (1) was prepared from the hydrochloride salts of naltrexone (13) and of methylhydrazine by the Piloty synthesis. The yields of these bivalent ligands ranged from 40–60%.

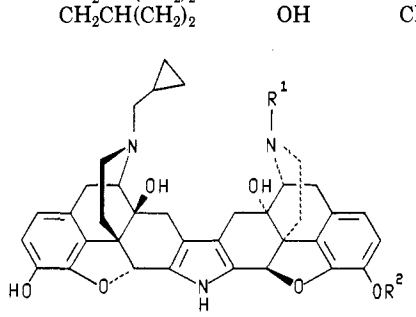
The tetraacetate ester 7 was prepared in 91% yield by allowing a mixture of nor-BNI and acetic anhydride in pyridine to stand for 2 days at 24 °C. The facility with which this acylation occurred is most likely due to an intramolecular transfer of an N-17 acylonium group to the neighboring axial 14-OH group. The diacetate 8 was readily obtained (93% yield) by base-catalyzed methanolysis.

The dimethyl ether 9 was obtained in 75% yield by treatment of 2 with excess methyl iodide in the presence of diisopropylamine. The corresponding monomethyl ether 10 was prepared (56%) by treating a methanolic solution of 2 with excess diazomethane. Surprisingly, the dimethyl ether 9 was a minor (28%) rather than a major product under these conditions.

Bivalent ligand 11, containing an agonist and antagonist pharmacophore, was synthesized from a near-equimolar mixture of the hydrochloride salts of naltrexone (13) and hydromorphone (16) in the presence of *N*-aminosuccin-



	R^1	R^2	R^3
3	$CH_2CH{=}CH_2$	OH	H
4	CH_3	OH	H
5	CH_3	H	H
6	CH_3	H	CH_3
7	$CH_2CH(CH_2)_2$	OAc	Ac
8	$CH_2CH(CH_2)_2$	OAc	H
9	$CH_2CH(CH_2)_2$	OH	CH_3



10: $R^1 = CH_2CH(CH_2)_2$; R^2 = OH; R^3 = Me
11: $R^1 = CH_3$; $R^2 = R^3$ = H

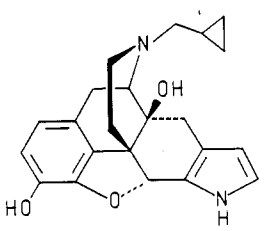


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Table I. Opioid Agonist Activities of 4–6

compd	GPI IC_{50} ± SE,[a] nM	GPI RP[b]	MVD IC_{50} ± SE,[a] nM	MVD RP[b]
4	250 ± 20 (4) 2630 ± 110 (4)[c]	0.2	170 ± 30 (3)	0.0008
5	53 ± 8 (3)	3.1	52 ± 6 (3)	0.002
6	330 ± 60 (3)	0.2	1000 ± 70 (3)	0.0004

[a] Number of experiments in parentheses. [b] Relative potency in the same tissue preparation (morphine = 1 in the GPI and DADLE = 1 in the MVD). [c] GPI was treated with 200 nM β-FNA for 60 min and the IC_{50} redetermined.

imide hydrochloride. The desired compound **11** was obtained in a yield of 25%, and the expected dimers **2** and **5** were produced in yields of 19% and 12%, respectively.

The monovalent pyrrole compound **12** was synthesized by refluxing a DMF–benzene solution of **13** and aminoacetaldehyde diethyl acetal in the presence of methanesulfonic acid.

TLC in two different solvent systems was employed as the primary criterion of purity because the compounds were heavily solvated with water and retained excess HCl as the salt.

Pharmacology. The agonist and antagonist activities were evaluated with the guinea pig ileal longitudinal muscle preparation (GPI) and the mouse vas deferens preparation (MVD), which were described in detail previously.[12] Molar concentrations employed in testing were based on the molecular weight of the fully solvated compounds.

Only those compounds with an *N*-methyl substitution (**4–6**) possessed weak but definite full agonist activity (Table I). The rest of the compounds with either an *N*-cyclopropylmethyl or an *N*-allyl substitution displayed either feeble partial agonist or no agonist activity. One of the full agonists (**4**) was tested on the β-FNA-treated GPI, a preparation devoid of functional μ receptors,[12,13] and its IC_{50} was shifted by a factor of 11 to higher concentration (Table I).

Most of the compounds under study had κ antagonist potency or κ selectivity that were inferior to those of **1** (BNI) or **2** (nor-BNI) (Table II). Only **3**, **8**, and **10** displayed κ-selective antagonism comparable to those of BNI and nor-BNI. Although **3** was about 6.5 and 2 times less potent than BNI and nor-BNI, respectively, it had clearly a higher selectivity for the κ receptor than BNI or nor-BNI. Compound **8** possessed κ antagonist potency equivalent to that of nor-BNI; it had a κ selectivity profile that was better against μ receptors and slightly poorer against δ receptors. Compound **10** was approximately 3 times less potent than nor-BNI and had a selectivity profile almost identical with that of nor-BNI. Significantly, **12** displayed an antagonist profile that was μ selective.

Discussion

BNI (**1**) and nor-BNI (**2**) possess C_2 symmetry. The three-dimensional structure of **2** (Figure 1) illustrates the anti orientation of the aromatic rings in this dimer and the fact that each of the basic nitrogens reside on one side of the molecule while the two phenolic hydroxyls are situated on the opposite side.[14] As this arrangement initially suggested to us the possibility that κ recognition sites may face each other on adjoining edges of identical or homologous subunits of the κ receptor system, we wished to evaluate this possibility. Accordingly, we explored the effect of structural modification on the κ opioid receptor selectivity of ligands in this series. Of primary interest was (1) the effect of substitutions on the two basic nitrogens, (2) the effect of blocking the phenolic OH groups, and (3) the role of the pyrrole ring.

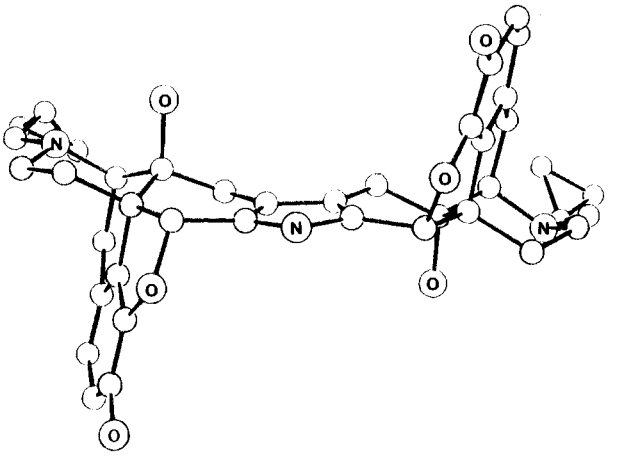

Figure 1. Structure of nor-BNI dihydrochloride.

The results of the present study demonstrate that the key structural features of the bimorphinans that contribute to the κ opioid receptor antagonist selectivity and potency are the presence of at least one free phenolic hydroxyl group and an appropriate substituent on one of the basic nitrogens. Thus, compounds whose phenolic groups are both blocked by acetylation (**7**) or methylation (**9**) were virtually inactive, while the corresponding singly methylated phenol **10** exhibited κ antagonist potency and selectivity that are very similar to that of nor-BNI (**2**). The importance of the basic nitrogen substitution was illustrated by the fact that compounds (**1–3**, **8**, **10**) having two *N*-cyclopropylmethyl or *N*-allyl groups possess potent κ opioid antagonist activity and selectivity. Interestingly, compound **11**, which contains only one cyclopropylmethyl group, possessed significant κ selectivity, but of somewhat lower magnitude. In this regard, it can be noted that *N*-methyl disubstituted compounds (e.g., **4** and **5**) are devoid of antagonist activity.

The 14-OH group apparently is unimportant for antagonist activity, as it was found that diacetate ester **8** is as potent as nor-BNI (**2**). In fact, this modification appeared to enhance selectivity over that of nor-BNI.

That the pyrrole moiety appears to be functioning primarily as a spacer was suggested by the lack of κ antagonist selectivity of the pyrrole monovalent ligand **12**. Although **12** is a potent κ antagonist, it is a μ-selective ligand. This suggests that the pyrrole moiety may not be an important contributor to κ selectivity and that any isosteric ring can serve as a spacer in its place.

Three members (**4–6**) of the series that contain agonist pharmacophores were found to have full agonist activity. This raised the question regarding the receptor type involved in mediating agonist activity. In order to answer this question, **4** was evaluated on a GPI preparation that had been depleted of functional μ receptors and thus contained only κ receptors. The 11-fold increase in the IC_{50} of **4** indicated that it is primarily a μ agonist. It seems likely that the other *N*-methyl compounds also have μ selectivity. This difference in selectivity between agonist and antagonist pharmacophores upon identical molecular modification may be due to the possibility of discrete agonist and antagonist recognition sites.[15]

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Table II. Opioid Antagonist Activities of Binaltorphimine and Its Analogues

		EK[a] (κ)		M[a] (μ)		DADLE[b] (δ)		selectivity ratio[c]	
compd	concn, nM	K_e[d]	IC_{50} ratio	K_e	IC_{50} ratio	K_e	IC_{50} ratio	μ/κ	δ/κ
1	20	0.14	148 ± 18	11	2.8 ± 0.7	5.7	4.5 ± 0.7	79	41
2	20	0.41	49.8 ± 7.8	13	2.6 ± 0.6	20	2.0 ± 0.1	32	49
3	100	0.91	111 ± 24	≥250	1.4 ± 0.6	≥143	1.7 ± 0.6[f]	≥275	≥157
4	20	e	1.6 ± 0.3	e	0.88 ± 0.18	e	1.1 ± 0.2		
5	10	e	0.79 ± 0.14	e	0.68 ± 0.63	e	0.85 ± 0.11[g]		
6	100	e	0.43 ± 0.07	e	0.51 0.07	e	0.93 0.04[g]		
7	100	e	1.6 ± 0.2	e	1.2 ± 0.1	e	1.4 ± 0.4		
8	100	0.38	261 ± 74	42	3.4 ± 0.4	12	9.2 ± 2.3	111	32
9	20	7.1	3.8 ± 1.0	e	0.8 ± 0	e	0.6 ± 0.1		
10	200	1.3	153 ± 30	38	6.3 ± 1.1	45	5.4 ± 1.6	29	35
11	200	1.9	108 ± 4	21	10.6 ± 4.8	41	5.9 ± 0.6	11	22
12	100	2.1	49.5 ± 5.6	0.65	155 ± 31	3.2	32.3 ± 8.1	0.3	1.5
naltrexone	100	5.5	19.3 ± 5.9	1.0	98 ± 24	24.4	5.1 ± 1.3	0.2	4.4

[a] Ethylketazocine (EK) or morphine (M) in the GPI. [b] [D-Ala^2,D-Leu^5]enkephalin in the MVD. [c] Calculated from K_e values. [d] K_e (nM) = [antagonist]/(IC_{50} ratio − 1), where IC_{50} ratio is IC_{50} of the agonist in the presence of the antagonist divided by the control IC_{50} in the same preparation ($n \geq 3$). [e] K_e not calculated because IC_{50} ratios for EK, M, and DADLE are all close to 1. [f] Conducted at 10 nM because of partial agonism (40% at 100 nM). [g] Twenty nanomolar in MVD.

Our basic assumption was that the enhanced κ opioid antagonist potency and selectivity of bivalent ligands **1–3**, **8**, **10**, and **11** relative to the monovalent analogue **12** are due to simultaneous occupation of proximal recognition sites (bridging) by both pharmacophores. These recognition sites may be (a) two neighboring opioid receptors, (b) two subsites of a single opioid receptor, or (c) an opioid site and a neighboring nonspecific site that is not part of the opioid recognition site. If possibility a exists, then two intact pharmacophores would be required in order to retain κ selectivity. On the other hand, possibilities b and c would not necessarily require an entire second pharmacophore.

Which of these possibilities (a–c) is responsible for conferring κ selectivity to BNI and related bivalent ligands remains to be rigorously determined. Although the nonselectivity of monomer **12** rules out the possibility of the pyrrole spacer as a major requirement for selectivity, it does not preclude any of the preceding possibilities. The fact that the K_e value of nor-BNI (**2**) is one-third that of the monomethyl ether **10** and about one-fifth that of the hybrid analogue **11** derived from naltrexone (**13**) and hydromorphone (**16**) suggests that the neighboring site favors an antagonist pharmacophore, but these modest differences might also be in part due to statistical factors (two versus one pharmacophore). The comparable κ selectivities of **2**, **10**, and **11** suggest that only one antagonist pharmacophore may be required and that some unknown moiety in the second half of the molecule confers selectivity. This may implicate the possibility b that two κ receptor subsites are involved; the first subsite recognizes the naltrexone-derived pharmacophore, and the second subsite permits binding of a moiety in the other half of the molecule. This neighboring subsite may be unique for the κ receptor system. Further studies are now under way to evaluate this model.

Experimental Section

Melting points were determined in open capillary tubes with a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. IR spectra were obtained on a Perkin-Elmer 281 infrared spectrometer. NMR spectra were recorded at ambient temperature on IBM-Bruker AC-300 with Me_2SO-d_6 and $CDCl_3$ as solvents and Me_4Si as internal standard. Mass spectra were obtained on a VG7070EHF instrument. Optical rotations were determined with a Perkin-Elmer 141 polarimeter. All TLC data were determined with Analtech, Inc. silica gel GHLF 21521, and the eluents $CHCl_3$–MeOH–NH_4OH or *n*-BuOH–AcOH–H_2O are denoted by CMA and BAW, respectively. Unless otherwise stated, all reagents and solvents were reagent grade and used without subsequent purification.

***N*-Aminosuccinimide Hydrochloride.** To a stirred solution of *tert*-butyl carbazoate (13.2 g, 0.1 mmol) in ethyl acetate (100 mL) was added succinic anhydride (10.0 g, 0.1 mmol) in an ice bath, and the mixture was stirred for 30 min at this temperature and then at 24 °C for 2 h. The reaction mixture was cooled in an ice bath, and to this was added *N*,*N*′-dicyclohexylcarbodiimide (DCC) (21.0 g, 0.1 mmol). After the mixture was stirred at 24 °C for 24 h, the precipitate was filtered and washed with ethyl acetate, and the solvent was removed to give the crude *N*-aminosuccinimide, mp 142–144 °C. To an ethyl acetate (50 mL) solution of the product was added 4 N HCl–EtOAc. The precipitate was filtered, washed with ethyl acetate, and dried over sodium hydroxide to give *N*-aminosuccinimide hydrochloride (12.3 g, 82%), mp >250 °C. Anal. ($C_4H_6N_2O_2$·HCl) C, H, N.

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). A solution of (−)-naltrexone hydrochloride (**13**·HCl) (377 mg, 1 mmol) and methylhydrazine hydrochloride (60 mg, 0.5 mmol) in DMF (3 mL) was heated on a steam bath for 2 h. After addition of 10% sodium bicarbonate solution (50 mL) to the cooled reaction mixture, it was extracted with EtOAc (three times). The combined organic phases were concentrated to dryness to give a crude product that was purified on a silica gel column (EtOAc–NH_4OH–MeOH, 50:0.1:0–5) to afford pure product (141 mg, 42%): mp >280 °C dec; $[\alpha]^{25}_D$ −330° (*c* 1.0, MeOH); R_f, 0.60 for free base (CMA, 18:2:0.1) and 0.69 for dihydrochloride (BAW, 2:1:1); ^{1}H NMR ($CDCl_3$) δ 5.56 (1 H, s) (C_5), 3.72 (3 H, s); ^{13}C NMR ($CDCl_3$) δ 143.1 (C_4), 138.9 (C_3), 130.5 (C_{12}), 125.3 (C_{11}), 124.9 (C_6), 118.4 (C_1), 117.0 (C_2), 115.5 (C_7), 85.0 (C_5), 73.1 (C_{14}), 62.2 (C_9), 59.3 (C_{18}), 48.0 (C_{13}), 43.6 (C_{16}), 31.7 (NMe), 30.6 (C_{15}), 28.8 (C_8), 23.0 (C_{10}), 9.3 (C_{19}), 4.0 (C_{20}), 3.7 (C_{21}); FABMS, *m*/*z* 676 (M^+ + H). Anal. ($C_{41}H_{45}N_3O_6$·3HCl·4.5H_2O) C, H, N.

17,17′-Bis(cyclopropylmethyl)-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′,14,14′-tetrol (2). Method A. A solution of naltrexone hydrochloride (**13**·HCl) (377 mg, 1 mmol) and *N*-aminosuccinimide hydrochloride (150 mg, 1 mmol) in DMF (2 mL) was stirred at 90 °C for 1 h. To this solution was added sodium bicarbonate solution (10%) in an ice bath, and the mixture was extracted (three times) with EtOAc. The combined organic phases were washed with brine, dried, and concentrated to give a crude product, which was purified on silica gel column (EtOAc–NH_4OH–MeOH, 50:0.1:0–5). The product so obtained was converted to its hydrochloride, which was rechromatographed (Sephadex, LH-20; MeOH) to afford pure **2**·2HCl (245 mg, 60%): mp >280 °C dec; $[\alpha]^{25}_D$ −377° (*c* 1.0, MeOH); R_f, 0.36 for free base (CMA, 18:2:0.1) and 0.46 for hydrochloride (BAW, 2:1:1); ^{1}H NMR (DMSO-d_6) δ 5.50 (1 H, s) (C_5); ^{13}C NMR (DMSO-d_6) δ 143.4 (C_4), 140.4 (C_3), 129.2 (C_{12}), 124.7 (C_{11}), 121.3 (C_1), 118.5 (C_6), 117.8 (C_7), 113.8 (C_2), 83.2 (C_5), 72.1 (C_{14}), 61.2 (C_9), 56.7 (C_{18}), 46.0 (C_{13}), 45.6 (C_{16}), 29.0 (C_{15}),

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28.2 (C_8), 5.7 (C_{19}), 5.0 (C_{20}), 2.7 (C_{21}); FABMS for free base, m/z 660.1 ($M^+ - 1$), 662.2 ($M^+ + 1$). Anal. ($C_{40}H_{43}N_3O_6 \cdot 2HCl \cdot 4H_2O$) C, N, Cl.

Method B. Naltrexone hydrochloride (3.0 g, 7.9 mmol) was dissolved in DMF (60 mL) at 100 °C. To the stirred solution under nitrogen was added hydrazine dihydrochloride (0.42 g, 4.0 mmol) suspended in DMF (5 mL). Stirring at 100 °C was continued for 6 h and then the solvent was replaced with 30 mL of DMSO. $MeSO_3H$ (0.38 g, 4.0 mmol) was added, and the mixture was stirred at 130 °C for 3 h. The cooled solution was diluted with an equal volume of H_2O, basified with excess NH_4OH, and extracted five times with an equal volume of EtOAc. The combined EtOAc extracts were washed twice with saturated NaCl solution and dried (anhydrous $MgSO_4$). The dried extract was concentrated to half volume and treated with a minimum amount of Florasil to remove the majority of color. The EtOAc solution was concentrated to one-fourth volume to promote precipitation of a portion of the base **2** (1.0 g). This was isolated by centrifugation and washed twice with EtOAc–Et_2O (50:50). The remainder of base was purified by preparative HPLC (Dynamax silica gel, 8 μm, column, 21.4 mm i.d. × 25 cm; EtOAc–MeOH–NH_4OH, 88:12:1, at 9 mL/min; 254 nm, product t_R = 27 min) to furnish an additional 790 mg (69% overall) of **2**. The base was converted to the hydrochloride salt with methanolic HCl. The physical and spectral properties of the salt were identical with those reported above.

17,17′-Diallyl-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′,14,14′-tetrol (3). Compound **3** was prepared from naloxone hydrochloride (**14**·HCl) in 75% yield via the procedure (method A) employed for the synthesis of **2**. The free base was chromatographed on a silica gel (100–200 mesh) with chloroform saturated with NH_4OH and a MeOH gradient (2–10% v/v). After the base was converted to the dihydrochloride salt, it was subjected to gel filtration on Sephadex LH20 in MeOH to afford pure product: mp >280 °C dec; R_f, 0.21 (CMA, 18:2:0.1) and 0.21 (BAW, 4:1:1). Anal. ($C_{38}H_{39}N_3O_6$) C, H, N.

17,17′-Dimethyl-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′,14,14′-tetrol (4). Oxymorphone hydrochloride (**15**·HCl) (300 mg, 1 mmol) was converted to **4** via the *N*-aminosuccinimide procedure as described for **2**. The reaction product **4** was chromatographed on a silica gel column (EtOAc–NH_4OH–MeOH, 50:0.1:0–5). After being converted to the dihydrochloride, the compound purified further on a Sephadex (LH-20, MeOH) column to afford 218 mg (60%) of **4**·2HCl: mp >280 °C dec; $[\alpha]^{25}_D$ −377° (*c* 1.0, MeOH); R_f, 0.21 for free base (CMA, 18:2:0.1) and 0.25 for dihydrochloride (BAW, 2:1:1); ^1H NMR (DMSO-d_6) δ 5.45 (1 H, s); ^{13}C NMR (DMSO-d_6) δ 143.4 (C_4), 140.5 (C_3), 129.1 (C_{12}), 124.7 (C_{11}), 121.4 (C_6), 118.6 (C_1), 117.8 (C_2), 113.7 (C_7), 83.2 (C_5), 72.3 (C_{14}), 65.5 (C_9), 46.4 (C_{13}), 45.4 (C_{16}), 41.0 (C_{18}), 38.7 (C_{15}), 28.9 (C_{10}), 28.3 (C_{18}). Anal. ($C_{34}H_{35}N_3O_6 \cdot 2HCl \cdot 4H_2O$) C, H, N; Cl: calcd, 9.76; found, 10.26.

17,17′-Dimethyl-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′-diol (5). Hydromorphone hydrochloride (**16**·HCl) (320 mg, 1 mmol) was converted to **5** via the *N*-aminosuccinimide procedure as described for **2**. The reaction product **5** was chromatographed on a silica gel column (EtOAc–NH_4OH–MeOH, 50:0.1:0–5). After being converted to the dihydrochloride, the compound was purified further on a Sephadex (LH-20, MeOH) column to afford 188 mg (60%) of **5**·2HCl: mp >280 °C dec; $[\alpha]^{25}_D$ −366° (*c* 1.0, MeOH); R_f, 0.18 for free base (CMA, 18:2:0.1) and 0.29 for dihydrochloride (BAW, 2:1:1); ^1H NMR (DMSO-d_6) δ 5.50 (1 H, s) (C_5); ^{13}C NMR (DMSO-d_6) δ 143.5 (C_4), 140.3 (C_3), 127.1 (C_{12}), 125.3 (C_{11}), 122.0 (C_1), 118.9 (C_6), 117.5 (C_7), 115.2 (C_2), 83.7 (C_5), 60.0 (C_9), 46.5 (C_{13}), 41.5 (C_{16}), 40.5 (C_{18}), 38.5 (C_{14}), 38.4 (C_{15}), 32.9 (C_{10}), 25.5 (C_8). Anal. ($C_{34}H_{35}N_3O_4 \cdot 2.5HCl \cdot 4.5H_2O$) C, H, N, Cl.

17,17′-Dimethyl-3,3′-dimethoxy-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan] (6). Dihydrocodeinone (**17**·HCl) (300 mg, 1 mmol) was converted to **6** via the *N*-aminosuccinimide procedure as described for compound **2**. The reaction product **6** was chromatographed on a silica gel column (EtOAc–NH_4OH–MeOH, 50:0.1:0–5). After the compound was converted to the dihydrochloride, it was purified further on a Sephadex (LH-20, MeOH) column to afford 171 mg (48%) of **6**·3HCl: mp 280 °C dec; $[\alpha]^{25}_D$ −333° (*c* 1.0, MeOH); R_f, 0.48 for free base (CMA, 18:2:0.1), 0.29 for hydrochloride (BAW, 2:1:1); ^1H NMR (DMSO-d_6) δ 5.55 (1 H, s) (C_5); ^{13}C NMR (DMSO-d_6) δ 144.2 (C_4), 142.5 (C_3), 127.1 (C_{12}), 125.9 (C_{11}), 120.4 (C_1), 119.2 (C_2), 115.3 (C_6), 115.2 (C_7), 90.1 (C_5), 60.2 (C_9), 56.4 (C_{19}), 55.7 (C_{18}), 44.6 (C_{13}), 41.4 (C_{16}), 38.0 (C_{14}), 35.9 (C_{15}), 32.1 (C_{10}), 25.6 (C_8). Anal. ($C_{36}H_{39}N_3O_4 \cdot 3HCl \cdot 3.5H_2O$) C, H, N, Cl.

17,17′-Bis(cyclopropylmethyl)-3,3′,14,14′-tetraacetoxy-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan] (7). A solution of **2**·HCl (62 mg, 0.084 mmol) in acetic anhydride (10 mL) and pyridine (10 mL) was allowed to stand at 24 °C for 2 days. The mixture was concentrated to dryness in vacuo, and to the residue was added ethyl acetate. The resulting solid was filtered and washed with EtOAc (two times) and hexane and dried at 110 °C in vacuo to afford **7**·2HCl (70.1 mg, 91%): mp 210 °C dec; R_f, 0.57 for hydrochloride (BAW, 2:1:1). Data for free base: IR (KBr, cm^{-1}) 1771, 1735, 1625; ^1H NMR ($CDCl_3$) δ 0.07 (4 H, m), 0.48 (4 H, m), 0.76 (2 H, m), 1.65 (2 H, m), 1.92 (6 H, s), 2.21 (6 H, s), 2.70 (2 H, dd, J = 8.0 Hz, 6.0 Hz), 3.12 (2 H, d, J = 18.8 Hz), 3.21 (2 H, d, J = 16.6 Hz), 4.48 (2 H, d, J = 5.5 Hz), 5.51 (2 H, s), 6.64 (2 H, d, J = 8.2 Hz), 6.78 (2 H, d, J = 8.2 Hz); FABMS; m/z 830 ($M^+ + 1$). Anal. ($C_{48}H_{51}N_3O_{10} \cdot 2HCl$) C, H, N.

17,17′-Bis(cyclopropylmethyl)-14,14′-diacetoxy-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′-diol (8). A mixture of **7**·2HCl (45 mg) and saturated sodium bicarbonate (1 mL) in MeOH (2 mL) was allowed to stand at 24 °C for 20 min. After the precipitate was filtered, the filtrate was extracted with EtOAc (three times). The combined organic phases were washed with brine, dried, and concentrated to give crude product, which was purified by preparative TLC (silica gel; 20% MeOH–$CHCl_3$) to afford pure **8** (38 mg, 93%): R_f, 0.24 (10% MeOH–$CHCl_3$); IR (KBr, cm^{-1}) 3350, 1735, 1637, 1616; ^1H NMR ($CDCl_3$) δ 0.06 (4 H, m), 0.47 (4 H, m), 0.16 (2 H, m), 0.76 (2 H, m), 1.83 (6 H, s), 3.07 (2 H, d, J = 18.4 Hz), 3.28 (2 H, d, J = 16.1 Hz), 4.45 (2 H, d, J = 5.2 Hz), 5.65 (2 H, s), 6.48 (4 H, s); FABMS, m/z 746 ($M^+ + 1$), 744 ($M^+ - 1$). Data for **8**·2HCl: R_f, 0.57 (BAW, 2:1:1); mp >250 °C dec.

17,17′-Bis(cyclopropylmethyl)-3,3′-dimethoxy-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-14,14′-diol (9). To a solution of **2**·2HCl (82 mg, 0.1 mmol) in DMF (0.5 mL) were added methyl iodide (0.45 mL) and diisopropylamine (0.6 mmol), and the mixture was stirred at 90 °C for 6 h. Sodium bicarbonate solution (10%) was added, and the mixture was extracted with EtOAc (three times). The combined organic phases were washed with ammonium hydroxide (10%) (three times) and with water and dried, and the solvent was removed in vacuo. The solid was converted to the dihydrochloride and purified on a Sephadex column (LH-20, MeOH) to afford the pure dihydrochloride (62.5 mg, 75%): mp >280 °C dec; R_f, 0.94 for free base (CMA, 18:2:0.1) and 0.46 for dihydrochloride (BAW, 2:1:1); ^1H NMR (DMSO-d_6) δ 5.50 (1 H, s) (C_5), 3.81 (6 H, s) (OMe); FABMS, m/z 690 ($M^+ + H$). Anal. ($C_{47}H_{47}N_3O_6 \cdot 2HCl \cdot 4H_2O$) C, H, N.

17,17′-Bis(cyclopropylmethyl)-3-methoxy-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3′,14,14′-triol (10). To a stirred solution of **2** (350 mg, 0.35 mmol) in methanol (10 mL) was added a large excess of ethereal diazomethane. After the mixture was allowed to stand 10 min at 24 °C, the solvent was removed to give an oil. Purification was effected by preparative TLC (silica gel; 20% MeOH–saturated NH_4OH–$CHCl_3$) to afford the monomethyl ether **10** (200 mg, 56%) and dimethyl ether **9** (100 mg, 28%). Data for **10**: R_f, 0.71 (CMA, 18:2:0.1); IR (liquid film, cm^{-1}) 3350, 3080, 3050, 2930, 2840, 1640, 1610, 1505; ^1H NMR ($CDCl_3$) δ 0.13 (4 H, m), 0.54 (4 H, m), 0.85 (2 H, m), 1.68 (2 H, d, J = 9.2 Hz), 2.10–3.00 (complex pattern), 3.07 (2 H, m), 3.20 (2 H, m), 3.80 (3 H, s), 5.48 (1 H, s), 5.02 (1 H, s), 6.48 (1 H, d, J = 8.1 Hz), 6.68 (2 H, d, J = 8.1 Hz), 6.55 (1 H, d, J = 8.1 Hz); FABMS, m/z 676.0 ($M^+ + 1$). Data for **10**·2HCl: R_f, 0.46 (BAW, 2:1:1). Anal. ($C_{41}H_{45}O_6N_3 \cdot 2HCl \cdot 2H_2O$) C, H, N. R_f value (CMA) and ^1H NMR spectra of the dimethylated product **9** were identical with that obtained by reaction of **2** and methyl iodide.

17-(Cyclopropylmethyl)-17′-methyl-6,6′,7,7′-tetradehydro-4,5:4′,5′-diepoxy-6,6′-(imino)[7,7′-bimorphinan]-3,3′,14-triol (11). A stirred solution of naltrexone hydrochloride (**13**·HCl) (100 mg, 0.26 mmol) and hydromorphone hydrochloride (**16**·HCl) (100 mg, 0.32 mmol) in DMF (3 mL) was mixed with

N-aminosuccinimide hydrochloride (200 mg, 1.33 mmol). The mixture was stirred at 100 °C for 18 h, and the solvent was removed in vacuo. The residue was treated with saturated sodium bicarbonate solution and chloroform and filtered, and the filtrate was extracted with chloroform (three times). The combined organic phases were washed with brine, dried, and concentrated to afford an oil that was purified on a Sephadex column (LH-20, MeOH) to give **11** (49 mg, 24.5%), **2** (38 mg, 19%), and **6** (24 mg, 12%). Data for **11**: R_f 0.23 (CMA, 18:2:0.1); ^{1}H NMR ($CDCl_3$) δ 0.10 (2 H, m), 0.51 (2 H, m), 0.82 (1 H, m), 1.70–2.80 (complex pattern), 2.32 (3 H, s), 2.90–3.30 (complex pattern), 5.42 (2 H, s), 5.42 (2 H, s), 6.20–6.80 (complex pattern); FABMS, m/z 606.0 ($M^+ - 1$). Data for **11**·2HCl: R_f 0.40 (BAW, 2:1:1). Anal. ($C_{37}H_{38}O_6N_3$·2HCl·3.4H_2O) C, H, N.

17-(Cyclopropylmethyl)-6,7-dehydro-4,5α-epoxy-3,14-dihydroxy-6,7,2′,3′-pyrrolomorphinan (12). To a stirred solution of naltrexone hydrochloride (**13**·HCl) (150 mg, 0.40 mmol) in benzene (10 mL) and DMF (10 mL) were added aminoacetaldehyde diethyl acetal (0.1 mL, 0.95 mmol) and methanesulfonic acid (0.05 mL, 0.5 mmol). The resulting mixture was stirred under reflux with Dean–Stark trap for 14 h. Ethyl acetate and saturated sodium bicarbonate solution were added to the mixture. The resulting mixture was filtered, and the filtrate was extracted with $CHCl_3$ (three times). The combined organic phases were washed with brine, dried, and concentrated to give a crude product that was purified by preparative TLC (silica gel, 10% MeOH–saturated NH_4OH–$CHCl_3$) to afford pure **12** (72.3 mg, 50%): R_f 0.06 (CMA, 19:1:0.1); IR (KBr, cm^{-1}) 3373, 2932, 1644, 1616; ^{1}H NMR (DMSO-d_6) δ 0.08 (2 H, m), 0.50 (2 H, m), 0.85 (1 H, m), 1.50 (1 H, m), 3.05 (1 H, d, J = 18.5 Hz), 3.18 (1 H, d, J = 5.3 Hz), 5.15 (1 H, s), 5.70 (1 H, t, J = 2.3 Hz), 6.45 (1 H, d, J = 8.1 Hz), 6.52 (1 H, d, J = 8.1 Hz), 6.68 (1 H, t, J = 2.6 Hz); CIMS, m/z 365 ($M^+ + 1$). Data for **12**·HCl: R_f 0.66 (BAW, 2:1:1); mp >330 °C dec. Anal. ($C_{22}H_{24}O_3N_2$·HCl·1.5H_2O) C, H, N, Cl.

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3-Phenoxypyridine 1-Oxides as Anticonvulsant Agents

Michael R. Pavia,*† Charles P. Taylor,‡ Fred M. Hershenson,† Sandra J. Lobbestael,† and Donald E. Butler†

Departments of Chemistry and Pharmacology, Parke-Davis Pharmaceutical Research Division, Warner-Lambert Company, Ann Arbor, Michigan 48104. *Received October 13, 1987*

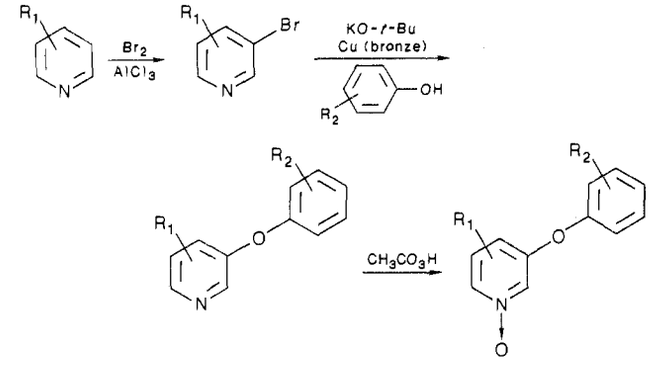
The anticonvulsant activity of a series of 3-phenoxypyridine 1-oxides is described. An investigation carried out to optimize the activity/side effect ratio provided 4-methyl-3-phenoxypyridine 1-oxide, **3**, as the derivative of choice. Overall, **3** has a pharmacological profile that is very similar to phenytoin. It exhibited significant anticonvulsant activity at doses that did not produce ataxia or sedation but caused increased spontaneous behavioral activity not seen with most anticonvulsants. The short duration of pharmacological effect of **3** was attributed to metabolic hydroxylation at the C-4 pyridine methyl group; however, structural modifications designed to inhibit this metabolic pathway were unsuccessful.

The search for new anticonvulsant drugs continues to be an active area of investigation in medicinal chemistry. Since currently available antiepileptic drugs are effective in only 60–80% of patients, there is a real need for improved agents.[1] Absence (petit mal) seizures are well treated in most instances, but significant therapeutic improvement is required for the treatment of partial-complex (focal) and generalized tonic–clonic (grand mal) seizures.[2] In addition, most marketed anticonvulsants suffer from a broad range of undesirable side effects[3] such as sedation, teratogenicity, cognitive dulling, blood dyscrasia, and hepatotoxicity. Failure to achieve control of seizures is frequently due to use-limiting side effects seen with increasing doses of these drugs before a satisfactory therapeutic dose is reached.

In collaboration with the NIH–NINCDS Antiepileptic Drug Development Program,[4] we have recently discovered the potent anticonvulsant effects of a series of substituted 3-phenoxypyridine 1-oxides.[5,6] While phenoxypyridine derivatives have been reported to possess a diverse range of biological properties,[7-13] the 3-phenoxypyridine 1-oxides described here have not previously been reported to possess anticonvulsant activity.

Initially, three compounds (**1–3**, Table I) were identified to possess anticonvulsant properties. While each of these compounds was effective in blocking seizures induced by maximal electroshock (an accepted model for generalized tonic–clonic seizures), **3** displayed the best overall profile. With 4-methyl-3-phenoxypyridine 1-oxide as a starting point, we systematically examined structural modifications

Scheme I



with the goal of increasing the potency, protective index, and duration of action of **3**.

† Department of Chemistry.
‡ Department of Pharmacology.

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