Synthesis and Evaluation of 3-Substituted 17-Methylmorphinan Analogs as Potential Anticonvulsant Agents†

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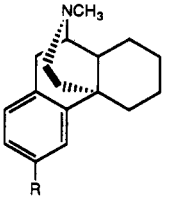
Dextromethorphan (1, (+)-3-methoxy-17-methylmorphinan) demonstrates anticonvulsant activity in a variety of in vitro and in vivo models of convulsive action. It is well known that 1 is metabolized to its phenolic derivative dextrorphan (2) and this metabolite is also a potent anticonvulsant. A series of (+)-3-substituted-17-methylmorphinans, which are structurally similar to 1 but are either not expected to be metabolized to 2 or might do so at a reduced rate, as compared to 1, were prepared. Three analogs, 5 ((+)-3-amino-17-methylmorphinan), 14 ((+)-3-ethoxy-17-methylmorphinan), and 15 ((+)-3-(2-propoxy)-17-methylmorphinan) were found to possess potent anticonvulsant activity with full efficacy (ED_{50} 25, 5.6, and 3.9 mg/kg, sc, respectively) in the rat supramaximal electroshock (MES) test. Binding potencies of these compounds to receptor sites labeled with [^{3}H]dextromethorphan ([^{3}H]1), in rat brain and guinea pig brain subcellular fractions, and [^{3}H]thienylcyclohexylpiperidine (TCP) and [^{3}H]glycine in rat brain, were determined. Most of the analogs displaced [^{3}H]1 from its binding sites, with compounds 14 (IC_{50} 0.42 μM) and 15 (IC_{50} 0.88 μM) having equivalent potencies to 1 (IC_{50} 0.59 μM), in rat brain, and no appreciable activity at the [^{3}H]TCP or [^{3}H]glycine-labeled sites. Compound 5 did not bind with appreciable activity to the [^{3}H]1 site, in rat brain, but did bind to the [^{3}H]TCP site with lower potency than the parent 1 (IC_{50} 7.8 and 2.0 μM, respectively). The mechanism of anticonvulsant action of these agents is not clear although it appears that interaction at the [^{3}H]1 sites may be involved.

Dextromethorphan (1, (+)-3-methoxy-17-methylmorphinan) is a nonopioid antitussive agent that is the active ingredient in many over-the-counter cough suppressants.[1] Evaluation in the rat supramaximal electroshock (MES) test, a seizure model sensitive to anticonvulsants effective in the treatment of partial and grand mal epilepsies,[2,3] showed that 1 was anticonvulsant and potentiated the anticonvulsant activity of the prototypic antiepileptic drug diphenylhydantoin.[4] More recently, the anticonvulsant activity of 1 has been demonstrated in a variety of in vitro and in vivo models of convulsive activity.[1] Furthermore, it has been noted that the protective index of 1 is significantly higher than many prototypical anticonvulsant drugs including phenytoin, phenobarbital, carbamazepine, and several PCP-like agents (for review see ref 1).

Dextromethorphan is rapidly and largely (>90%) O-demethylated in vivo to the phenolic dextrorphan (2), in Sprague-Dawley rats[5] and in most (~90%) humans.[6,7] This metabolite has been shown to attenuate MES-induced convulsions in rats (7-fold more potent than 1 and 1.6-fold more potent than diphenylhydantoin).[4] Hence the anticonvulsant activity demonstrated by 1 may be attributed to its metabolite.[8] It has been contended that 1 may have subjective effects of a psychotomimetic nature in humans.[9] However, its behavioral actions in animals are clearly



1, R=OCH_3
2, R=OH

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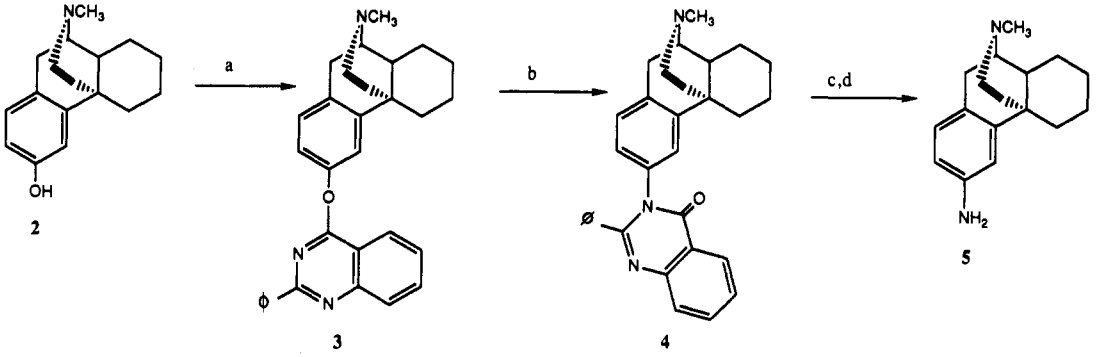
Scheme I [a]



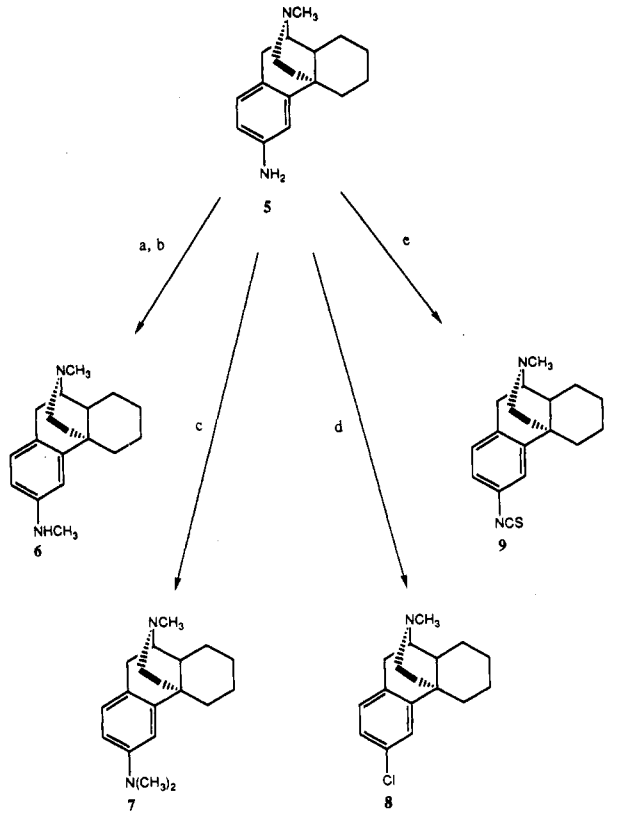
[a] (a) AM-ex-OL; (b) 330–350 °C; (c) 2 N NaOH, EtOH; (d) HCl.

different than **2** or PCP.[10,11] Furthermore these actions may be completely attributable to the metabolite **2** which has been shown in several animal models to mimic behaviors of known psychotomimetic drugs.[12-14]

We proposed a series of compounds based on **1** that would replace the 3-methoxy group with moieties that are not expected to be metabolized to **2**, or might do so at a reduced rate, as compared to **1**. If any of these synthetic analogs showed anticonvulsant activity, with equal or higher potency, then the implication would be that metabolism of **1** to **2** is not necessary for anticonvulsant action. Furthermore, in vivo and in vitro evaluation of this series of compounds may shed light on structure–activity relationships for anticonvulsant activity and may also provide new agents with which to study the mechanism of anticonvulsant action.

Chemistry. Synthesis of the target compounds **5–9** began with **2**, which was prepared by a standard O-demethylation of **1** (Sigma Chemical Co.) with 48% HBr, in quantitative yield. In Scheme I, treatment of **2** with 4-chloro-2-phenylquinazoline (Am-ex-OL, Aldrich Chemical Co.) in acetone resulted in excellent yields of the ether **3**. Heating **3**, neat, to 330–350 °C,[15] resulted in decomposition. Subsequently, it was discovered that using mineral oil as the solvent[16] resulted in successful conversion of **3** to **4** in moderate yield. Temperature regulation was critical for this reaction to proceed properly. If temperatures were below 330 °C, the reaction proceeded very slowly (3–5 days with significantly lower yields). If the reaction temperature was allowed to exceed 360 °C, the reaction mixture darkened and a large (30–40% by weight) amount of a highly fluorescent aromatic side product was isolated. Basic hydrolysis of **4** to an amadino–carboxylic acid intermediate was followed by acidic hydrolysis to the desired amine **5**. In Scheme II, monomethylation of **5** using 37% HCHO and succinimide followed by $NaBH_4$ reduction in DMSO[17] gave **6**. Dimethylation of **5** with 37% HCHO and $NaBH_3CN$[18] resulted in a good yield of **7**. Conversion of **5** to **8** was obtained by treating **5** with *tert*-butyl nitrite and $CuCl_2$ in MeCN.[19] Treatment of **5** with thiophosgene in a biphasic $CHCl_3$/aqueous $NaHCO_3$ system[20] gave an excellent yield of **9**. In Scheme III, conversion of **2** to the 3-(1-phenyl-1*H*-5-tetrazolyl) de-

Scheme II [a]



[a] (a) HCHO, succinimide; (b) $NaBH_4$; (c) HCHO, $NaBH_3CN$; (d) *t*-BuONO, $CuCl_2$; (e) Cl_2CS.

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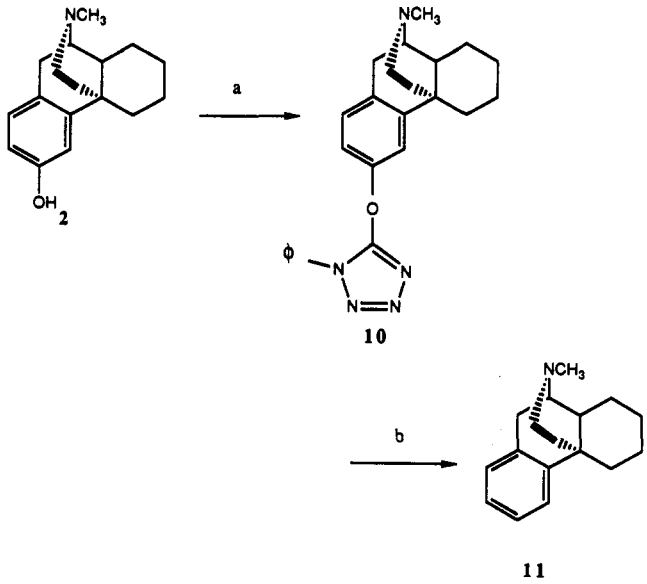
Scheme III [a]



[a] (a) 5-(Chlorophenyl)tetrazole; (b) H_2, 10% Pd/C.

rivative **10** by reaction with 5-chloro-1-phenyl-1*H*-5-tetrazole was followed by hydrogenolysis[21] to give **11**.

A series of alkyl ether derivatives (**14–17**) was prepared from *N*-desmethyldextromethorphan (**12**) from **1**, using 1-chloroethyl chloroformate (ACE-Cl),[22] as depicted in Scheme IV. N-Formylation using ethyl formate was followed by BBr_3 O-demethylation to give **13** in good yield. A general method of O-alkylation with the appropriate alkyl halide and $LiAlH_4$ reduction resulted in the desired O-alkyl derivatives **14–17**. Table I summarizes the physical properties of the compounds in this series.

Results and Discussion

In general, MES in rats causes a generalized convulsion characterized by an initial tonic extension of the forelimbs, progressing immediately to tonic hindlimb extension followed by clonic jerking. The presence or absence of tonic hindlimb extension is recorded for each MES convulsion. We have previously shown that the shock parameters used in this study induce MES, and not threshold seizures.[23]

In Table II, the anticonvulsant activity of **1**, **2**, and the synthetic analogs is shown. Compound **1** demonstrated anticonvulsant activity [ED_{50} 38 (95% CL, 19–74) mg/kg] and **2** was approximately 8 times more potent [ED_{50} 5 (95% CL, 1–28) mg/kg]. Compound **5** was equipotent to **1** [ED_{50} 25 (95% CL, 16–38) mg/kg], and compounds **14** and **15** were equipotent to **2** (ED_{50} 5.6 (95% CL, 2.9–10.7) and 3.9 (95% CL, 2.3–6.6)], respectively. At doses of 12.5, 25 and 40 mg/kg, compound **7** protected 30–40% of the rats from convulsing; at 50 and 100 mg/kg, no seizure protection was detected, demonstrating a nondose-related protection that never reached full efficacy. Likewise, compound **16** showed a maximum protection of 40% at 40 mg/kg; this degree of protection was also observed at 20 mg/kg and 10% and 30% of the animals were protected at 5 and 10 mg/kg, respectively.

A linear dose–response effect was observed for compounds **1**, **5**, **14**, and **15** (data not shown). Compound **1** was only 70% efficacious at its maximum dose; the dose of **1** cannot be increased due to the fact that it actually lowers convulsant thresholds at higher doses (100 mg/kg).[24] However, the synthetic analogs **5**, **14**, and **15** were all maximally efficacious. This maximal protection was achieved at a dose of 10 mg/kg for compounds **14** and **15** and at 50 mg/kg for compound **5**. Importantly, at maximum doses of these compounds, no signs of neurologic deficit such as ataxia, stereotypy, head weaving, or other behaviors associated with psychotomimetic agents were observed.

The anticonvulsant action of **1** has been demonstrated, but the mechanism of this action has not yet been elucidated. High- and low-affinity binding sites labeled with [^{3}H]**1** have been characterized in guinea pig and rat brain.[25–28] Further characterization of these sites with putative σ ligands has supported the existence of at least one common dextromethorphan/σ high affinity binding site.[29,30] Some but not all σ ligands demonstrate anticonvulsant activity;[24,1] hence it would be difficult to explain the anticonvulsant profile of **1** as being mediated solely through this common binding site.

Dextromethorphan (**1**) has also been described as a weak noncompetitive NMDA antagonist and many other agents in this class are anticonvulsant including PCP, MK 801, and ketamine.[31,32] The rank order of anticonvulsant potency of this class of drugs is similar to their relative affinities for PCP binding sites[33] that are associated with

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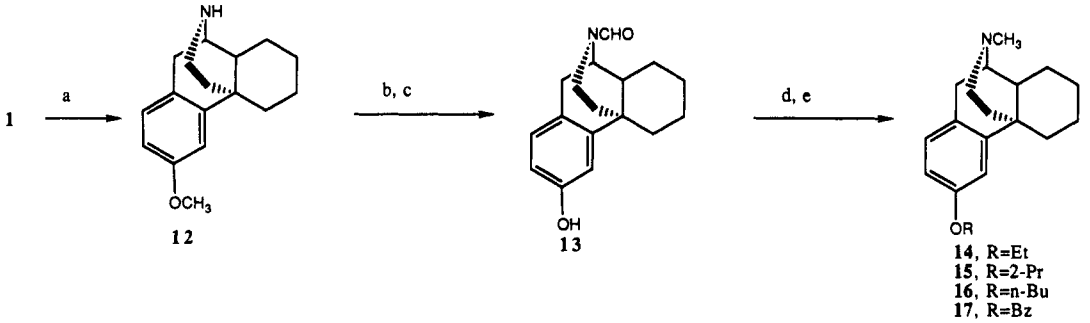
Scheme IV [a]



[a] (a) ACE-Cl; (b) EtOCHO; (c) BBr_3; (d) RX; (e) $LiAlH_4$.

Table I. Physical Properties of *O*-Alkyl Ether Derivatives

compd	molecular formula	rec solv	% yield	mp, °C	$[\alpha]_D$, (MeOH)
14	$C_{19}H_{27}NO \cdot HCl \cdot {}^1/_4H_2O$	EtOAc	67	233–235	29.52 (*c* 1.04)
15	$C_{20}H_{29}NO \cdot C_4H_4O_4$	MeOH/ether	79	181–185	22.75 (*c* 1.09)
16	$C_{21}H_{31}NO \cdot 1.5C_4H_4O_4$ [a]	2-PrOH	75	153–154	17.25 (*c* 1.15)
17	$C_{24}H_{29}NO \cdot HCl \cdot {}^1/_4H_2O$	2-PrOH	74	231–232	34.22 (*c* 0.64)

[a] HRMS (M^+) calcd for $C_{21}H_{31}NO$ 313.2405, found 313.2408.

Table II. Anticonvulsant Activity of Dextromethorphan Analogs in the Rat MES Test

compd	dose, mg/kg	% rats protected[a]	ED_{50} (95% CL), mg/kg, sc	ED_{50} (95% CL), μmol/kg
1	15–60	70	38 (19–74)	109 (54–211)
2	2.5–10	90	5 (1–28)	12 (3–69)
3	2.5–50	10		
5	12.5–50	100	25 (16–38)	76 (49–116)
6	25–100	0		
7	12.5–100	40[b]		
8	25–50	10		
9	25–50	0		
11	25–100	0		
14	1.25–25[c]	90	5.6 (2.9–10.7)	17.4 (9.0–33.2)
15	1.25–10	90	3.9 (2.3–6.6)	9.4 (5.5–15.9)
16	5–40	40		
17	50	30		

[a] n = 10 rats. [b] % protection at 40 mg/kg, 0% at higher doses. [c] 90% protection at 10 and 25 mg/kg.

the NMDA receptor–ion channel complex.[34] Furthermore, 1 has been shown by several groups to be an effective, albeit weak, inhibitor of seizures mediated by activation of NMDA receptors.[35–38]

In addition to the complicated binding profile of 1, it has been well established that it is quickly and largely metabolized to another anticonvulsant drug, 2.[5–7] This compound is a more potent anticonvulsant agent in the rat MES test and is a more potent NMDA antagonist than the parent 1.[8,36,39] Furthermore, 2 binds with a 100-fold lower affinity to [^{3}H]1-labeled sites than does 1[26] and 2 fails to mimic the effect of 1 in potentiating the anticonvulsant activity of diphenylhydantoin.[8] Thus the differences in the binding profiles of 1 and 2 and their different effects on potentiation of the anticonvulsant effects of diphenylhydantoin, suggest that 1 may produce its anticonvulsant effects through a mechanism that is not common to 2.[8,38]

In light of these reports, binding of 1, 2, and the present synthetic analogs to the dextromethorphan binding site and to the PCP and glycine sites associated with the *N*-methyl-D-aspartate (NMDA) receptor–channel complex was investigated using [^{3}H]1, [^{3}H]TCP, and [^{3}H]glycine as radioligands. The methods used were based on those reported in the literature, but have been optimized for the conditions detailed in the Experimental Section. In addition to the synthetic analogs, standards for each assay were also tested (1 for [^{3}H]1 binding, phencyclidine (PCP) for [^{3}H]TCP binding, and glycine for [^{3}H]glycine binding), as well as chlorpromazine (CPZ), MK 801, and dichlorokynurenic acid (DCK) in all five assays.

The results of the radioligand displacement studies are shown in Table III. None of the compounds tested were able to displace [^{3}H]glycine. In addition, DCK, a ligand reported to be more potent than glycine at the glycine binding site,[40] was inactive against [^{3}H]1, while being active at both [^{3}H]TCP and [^{3}H]glycine. All the compounds except 2 and 5 were less active against [^{3}H]TCP than against [^{3}H]1, in rat brain. The phenolic metabolite 2, displaced [^{3}H]1 from rat brain and guinea pig brain subcellular fractions with lower potency than 1. Moreover, compound 5 displaced [^{3}H]1 from these sites in the guinea pig, with lower potency than 1 or 2 and was unable to completely displace (45%) this radioligand at a concentration of 10^{-5} M, in the rat brain. It is unlikely that [^{3}H]1 is binding to the same site as [^{3}H]TCP, as neither MK 801 nor DCK produced much displacement of [^{3}H]1 binding. Conversely, several of the new analogs demonstrated high potency binding to the [^{3}H]1 site with little or no activity at the [^{3}H]TCP site. Several of the analogs appeared to

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Table III. Binding Data for Dextromethorphan Analogs[a]

compd	IC_{50}, μM				
	[^{3}H]1			[^{3}H]TCP:	[^{3}H]glycine:
	GP (P2)[b]	GP (P3)[c]	rat brain	rat SPM[d]	rat SPM
1	0.24 ± 0.06 (8)[e]	0.49 ± 0.12 (10)	0.59 ± 0.12 (10)	2.0 ± 0.6 (4)	NA[f] (4)
2	2.5 ± 0.4 (4)	2.7 ± 0.3 (5)	7.7 ± 0.9 (5)	1.2 ± 0.7 (4)	NA (4)
3	25% (4)	50% (4)	19% (5)	NA (4)	NA (6)
5	6.4 ± 2.8 (4)	4.4 ● 0.9 (5)	45% (5)	7.8 ± 1.4 (3)	NA (4)
6	0.48 ± 0.12 (4)	1.3 ± 0.7 (4)	3.6 ± 1.4 (5)	43% (4)	NA (4)
7	0.68 ± 0.13 (4)	1.1 ± 0.5 (5)	4.4 ± 0.9 (5)	45% (4)	NA (4)
8	0.37 ± 0.12 (4)	0.21 ± 0.03 (4)	1.1 ± 0.4 (5)	5.5 ± 1.5 (4)	NA (6)
9	0.44 ± 0.13 (4)	0.17 ± 0.01 (4)	1.5 ± 0.3 (5)	60% (4)	NA (6)
11	1.7 ± 0.3 (4)	1.0 ± 0.3 (5)	1.3 ± 0.3 (5)	53% (5)	NA (4)
14	0.09 ± 0.02 (4)	0.13 ± 0.03 (4)	0.42 ± 0.06 (5)	75% (4)	NA (5)
15	0.15 ± 0.05 (4)	0.12 ± 0.03 (4)	0.88 ± 0.18 (5)	59% (4)	NA (5)
16	0.16 ± 0.03 (4)	0.10 ± 0.04 (4)	1.5 ± 0.4 (5)	58% (4)	NA (5)
17	0.27 ± 0.07 (4)	0.15 ± 0.07 (4)	3.1 ± 0.6 (5)	39% (4)	NA (6)
CPZ	1.1 ± 0.10 (3)	0.60 ± 0.15 (4)	1.3 ± 0.2 (3)	25% (4)	NA (4)
MK 801	19% (4)	20% (4)	42% (3)	0.01 ± 0.003 (4)	10% (4)
DCK	NA (4)	NA (3)	NA (2)	2.4 ± 1.3 (4)	0.39 ± 0.35 (2)
PCP	NT[g]	NT	NT	0.18 ± 0.04 (7)	NT
glycine	NT	NT	NT	NT	0.69 ± 0.2 (9)

[a] IC_{50} values given are expressed in micromolar where a displacement curve was obtained, or in percent inhibition at 10^{-5} M where this was less than 50%, or where an abnormally high slope was obtained. [b] Guinea pig mitochondrial pellet. [c] Guinea pig microsomal pellet. [d] Synaptic plasma membrane. [e] *n* value = number of animals used. [f] No effect. [g] Not tested.

be more potent than 1 in the [^{3}H]1 binding assays, notably 14 in the rat brain, 14–16 in the guinea pig mitochondrial fraction, and 8, 9, 14–17 in the guinea pig microsomal fraction. All of these compounds appear to be quite selective for this binding site over the [^{3}H]TCP site. This is particularly interesting with regard to compound 9, an isothiocyanato derivative, and therefore a potential irreversible ligand, which may be useful in further characterizing this site. Notably, compound 5 demonstrated the lowest activity at this site in this series of compounds.

In general the compounds were more active in guinea pig than in rat brain, although this may reflect the fact that guinea pig brain was tested as P_2 and P_3 subcellular fractions and does not rule out the possibility that a compound may be active in either of these fractions in the rat brain. Compound 1 was reported[28] to be more active in the microsomal fraction of the guinea pig brain, although this was not reflected in the results obtained in these experiments. The reason for this is not clear, but may reflect that whole brain was used (high affinity [^{3}H]1 binding is enriched in specific brain regions especially pons medulla and cerebellum). It could be due to contamination of the preparation by other cell fractions, although this seems unlikely in view of the initial 40000*g* spin employed to isolate this fraction.

Summary

In this first series, compounds 5, 14, and 15 were protectant against MES-induced seizures. This initial screening suggests that the anticonvulsant activity of this series of compounds is dependent on the 3-position substituent and that minor modification can either improve or completely abolish activity. Elimination of the 3-methoxy group results in an inactive compound (11) and replacement with isosteres including the mono- and dimethylamino functionalities (6 and 7, respectively) and the chloro group (8) also resulted in inactive or less efficacious compounds. Although compound 9 was inactive as an anticonvulsant, due to the highly reactive nature of the isothiocyanate group, we cannot rule out that, administered systemically, it may not actually get into the brain. Further evaluation of the potential irreversible binding profile of this compound is in progress.

It is unlikely that the active compound 5 would be metabolized to 2. Compound 5 does not bind appreciably to the [^{3}H]1 site in rat brain, but does bind to this site with slightly lower potency than 2, in the guinea pig brain subcellular fractions. This compound does bind to the [^{3}H]TCP site and therefore this may account for its anticonvulsant action. However, compound 5 exhibits significantly lower potency at this site than compounds 1 and 2, despite its potent anticonvulsant profile. At this point, the distinction between compound 5 at [^{3}H]TCP and [^{3}H]1 binding sites appears small and insufficient to conclude the involvement of one but not the other in its anticonvulsant action. Clearly, further evaluation of this compound is necessary to elucidate its mechanism of action as well as its behavioral profile; i.e. does it resemble PCP-like drugs?

Evaluation of the alkyl ether series demonstrated that increasing the alkyl side chain size to ethyl or 2-propyl improved anticonvulsant potency. These compounds demonstrated equivalent binding potencies at the [^{3}H]1 site, as compared to 1. As the size of the alkyl chain was increased to *n*-butyl (16), benzyl (17), and a bulky heterocycle (3), anticonvulsant activity was diminished and ultimately abolished. Interestingly, high potency binding to the [^{3}H]1 sites was retained except when the very bulky heterocyclic group of compound 3 was appended. All of the other analogs showed selectivity for [^{3}H]1 sites over the [^{3}H]TCP sites. Since these compounds do not bind appreciably to the [^{3}H]TCP site, it is unlikely that the anticonvulsant properties of 14 and 15 can be attributed to their interactions there. The facts that both of these compounds are equipotent to 2 and do not produce observable behavioral side effects associated with this metabolite suggest that metabolism to 2 is not necessary for anticonvulsant action to take place. Studies are currently underway to investigate whether these compounds serve as substrates for the cytochrome P 450

(2D6) enzyme known to catalyze the O-demethylation of 1 (for review see ref 41).

In conclusion, this series of 3-substituted 17-methylmorphinans was prepared as potential new anticonvulsant agents, as tools to further characterize [^{3}H]1 binding sites and to ascertain whether a functional correlate exists between anticonvulsant activity and binding to these sites. Our data suggest that the 3-hydroxyl group of 2 is not necessary for anticonvulsant activity and that compounds 5, 14, and 15 represent novel anticonvulsants with improved efficacy over the parent drug. The mechanism of anticonvulsant action of these agents is not clear although it appears that interaction at the [^{3}H]1 site may be involved. Further in vivo and in vitro pharmacological evaluation of these compounds in other anticonvulsant and behavioral models is in progress.

Experimental Section

Synthesis. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Thin-layer chromatography (TLC, silica gel GF, Analtech, DE) was used to detect product homogeneity and $CHCl_3$/MeOH/NH_4OH (90:10:1) was the solvent system used unless otherwise indicated. Flash column chromatography (silica gel, grade 60, 230–400 mesh, Aldrich Chemical Co., Milwaukee, WI), was used for purification; the solvent system for chromatography was $CHCl_3$/MeOH/NH_4OH (90:10:1) unless otherwise specified. ^{1}H NMR spectra were obtained either on a Bruker AC 300-MHz or a Varian XL 300-MHz NMR spectrometer using trimethylsilane as an internal standard, ^{13}C NMR spectra were obtained on a Bruker AC 300 MHz spectrometer. IR spectra were determined on a Nicolet Model 105 IR spectrophotometer using either KBr pellets or $CHCl_3$ cells. EIMS and CIMS (NH_3) were obtained on a Finnegan 1015 mass spectrometer. High-resolution mass measurements (HRMS) were obtained on a VG-Micro Mass 7070F mass spectrometer. All compounds exhibited NMR, IR, and mass spectral data consistent with those structures assigned. Optical rotation were obtained on a Jasco DIP-370 digital polarimeter at 23 °C. Elemental analyses were performed by either Spang Microanalytical Laboratory, Eagle Harbor, MI, or Atlantic Microlabs, Atlanta, GA, and were within 0.4% of theoretical values.

(+)-3-[(2-Phenyl-4-quinazolinyl)oxy]-17-methylmorphinan (3). Dextrorphan (2) was obtained in quantitative yield by a general method of O-demethylation of dextromethorphan HBr (1, Sigma) with 48% HBr, and was found to be identical by TLC, mp, and ^{1}H NMR to an authentic sample. By using a modification of the procedure by Conrow and Bernstein,[15] 2 (16.10 g, 62.3 mmol) was dissolved in hot acetone (500 mL); AM-ex-OL (15.51 g, 64.4 mmol, Aldrich Chemical Co.) and K_2CO_3 (17.13 g, 123.9 mmol) were added. The reaction mixture was allowed to stir at reflux, under an atmosphere of argon, overnight. After cooling, the reaction mixture was extracted from H_2O (500 mL) with benzene (1 × 500 and 2 × 250 mL), followed by washing the combined organics with H_2O (1 × 250 mL) and removing the solvent in vacuo, to give 27.51 g (96%) of 3 as a white glass which was homogeneous by TLC. Recrystallization in EtOAc gave pure 3 as white crystals: mp 138–139 °C; EIMS m/z 461; $[\alpha]_D$ +59.5 (c 1.03, acetone). Anal. ($C_{31}H_{31}N_3O$) C, H, N.

(+)-3-[4-Oxo-2-phenyl-3(4*H*)-quinazolinyl]-17-methylmorphinan (4). Compound 3 (10.0 g, 21.7 mmol) was placed in mineral oil[16] (100 mL, light white oil, Sigma Chemical Co.), under a stream of argon, and the vigorously stirring reaction mixture was carefully heated in a sand bath to 330–350 °C. Complete conversion of 3 to one major product spot occurred in 8–10 h. (Note: This reaction proceeds significantly slower at lower temperatures and will rapidly decompose at temperatures that exceed 360 °C.) The yellow reaction mixture was allowed to cool to room temperature and suction filtered through a pad of silica gel. The mixture was eluted with 700 mL of ether (to remove all mineral oil). Then, the receiving flask was changed, and the product was eluted with $CHCl_3$/MeOH/NH_4OH (800 mL, 90:10:1) to give 5.95 g of (60%) yellow foamy product that was homogeneous by TLC. This intermediate was not crystalline. It was characterized spectrally and taken to the next step without further purification: IR 1690 (C=O) cm^{-1}; EIMS m/z 461.

(+)-3-Amino-17-methylmorphinan Dihydrochloride (5). Sodium hydroxide (4 N, 30 mL) was added to a solution of 4 (4.89 g, 10.7 mmol) in absolute EtOH (100 mL), and the reaction mixture was allowed to stir at reflux, under an atmosphere of argon. After 18 h, TLC showed complete loss of 4. The reaction mixture was cooled in an ice bath and carefully acidified to pH 2 with concentrated HCl. Additional 1 N HCl (100 mL) was added and the reaction mixture was allowed to stir at reflux, under an atmosphere of argon for 1.5 h. After cooling in an ice bath, the aqueous reaction mixture was extracted with ether (1 × 200 and 2 × 100 mL). The ether fraction was washed with 1 N HCl (1 × 200 mL) and the combined aqueous fraction was neutralized to pH 9 with NH_4OH. Extraction with $CHCL_3$ (1 × 200 mL and 1 × 100 mL) followed by $CHCl_3$/MeOH (4:1, 1 × 100 mL) and removal of solvent in vacuo resulted in 2.53 g (93%) crude 5 as a white foamy free base. The free base was dissolved in a minimal volume of hot MeOH and acidified with a saturated solution of HCl in 2-PrOH. Addition of ether resulted in an oily product, but removal of solvent followed by recrystallization in MeOH/ether resulted in 1.0 g (34%) of 5 as white crystals, 280 °C dec. The mother liquor was neutralized and purified by flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:5:1) to give 0.84 g (31%) pure base as a white foam: IR (free base, $CHCl_3$) 3400 cm^{-1} (two sharp bands, NH_2); ^{1}H NMR ($CDCl_3$) δ 6.90 (d, J = 8.4 Hz, 1 H), 6.60 (d, J = 2.4 Hz, 1 H), 6.50 (dd, J = 8.4, 2.4 Hz, 1 H), 3.55 (brs, 2 H), 2.60 (s, 3 H); CIMS m/z 257 (M + 1); $[\alpha]_D$ +21.7 (c 0.53, MeOH). Anal. ($C_{17}H_{24}N_2$·2HCl) C, H, N.

(+)-3-(Methylamino)-17-methylmorphinan Dioxalate (6). Formaldehyde (37%, 0.30 mL) and succinimide (0.45 g, 4.5 mmol) were added[17] to a solution of 5 (0.76 g, 3 mmol, free base) in absolute EtOH (8 mL). The reaction mixture was allowed to stir at reflux, under an atmosphere of argon, for 2 h. The volatiles were evaporated, the residue was redissolved in DMSO (3 mL), and $NaBH_4$ (0.18 g, 4.7 mmol) was added, at room temperature. The reaction mixture was warmed to 100 °C, allowed to stir for 15 min, and cooled. Quenching with H_2O (25 mL) and extraction with CH_2Cl_2 (3 × 25 mL) was followed by washing the combined organics with H_2O (3 × 20 mL), drying (Na_2SO_4), and evaporating to give 0.50 g (63%) of an off white foam that was nearly homogeneous by TLC. The foamy free base was dissolved in a minimal volume of hot MeOH, and oxalic acid (0.33 g, 3.7 mmol, 2 equiv) was added (pH 4). The crystalline product was isolated and recrystallized in MeOH to give 0.51 g (61%) of 6: mp 187–193 °C; IR (salt, KBr) 2400 cm^{-1} (broad NH^+); ^{1}H NMR ($CDCl_3$) δ 6.92 (d, J = 8.4 Hz, 1 H), 6.50 (d, J = 1 Hz, 2.4 H), 6.43 (dd, J = 8.4, 2.4 Hz, 1 H), 2.78 (s, 3 H), 2.35 (s, 3 H); EIMS m/z 270; $[\alpha]_D$ +22.0 (c 1.08, MeOH). Anal. ($C_{18}H_{26}N_2$·$C_4H_4O_8$·$^1/_4H_2O$) C, H, N.

(+)-3-(Dimethylamino)-17-methylmorphinan Sesquitartrate (7). Formaldehyde (37%, 2.4 mL) and $NaBH_3CN$ (0.60 g, 13 mmol) were added at 0 °C[18] to a solution of 5 (0.52 g, 2 mmol, free base) in MeCN (10 mL). The reaction mixture (pH 12) was allowed to stir at 0 °C for 5 min and then allowed to warm to room temperature. After a reaction time of 30 min, glacial HOAc (0.3 mL) was added and the reaction mixture (pH 6) was allowed to stir at room temperature for another 45 min. The volatiles were removed in vacuo, and the residue was extracted with 2 N KOH (1 × 20 mL) and ether (4 × 10 mL). The combined organic fraction was washed with H_2O (1 × 10 mL), dried (Na_2SO_4), and evaporated to 0.53 g of a pale yellow oil (93%) which was nearly homogeneous by TLC. The crude free base was dissolved in hot 2-PrOH and added to a solution of D-(*l*)-tartaric acid (0.57 g, 4 mmol) in hot 2-PrOH. The crystalline 7 (0.67 g, 65%) was carefully isolated under an atmosphere of argon (hygroscopic): mp 96–99 °C; ^{1}H NMR ($CDCl_3$) δ 3.15 (s, 6 H); EIMS m/z 284; $[\alpha]_D$ +5.73 (c 0.96, MeOH). Anal. ($C_{19}H_{28}N_2$·$C_6H_9O_9$·$^1/_4H_2O$) C, H, N.

(41) Eichelbaum, M.; Gross, A. S. The genetic polymorphism of debrisoquine/sparteine metabolism—clinical aspects. *Pharmacol. Ther.* **1990**, *46*, 377–394.

(+)-3-Chloro-17-methylmorphinan Fumarate (8). Acetonitrile (16.0 mL), *tert*-butyl nitrite (0.8 mL, 90%, 5.4 mmol), and dried $CuCl_2$ (0.68 g, 5.0 mmol) were combined and warmed to 60 °C,[19] in an argon-purged round-bottom flask. A solution of **5** (1.0 g, 4 mmol, free base) in MeCN (8.0 mL) was added dropwise, via addition funnel, over 10 min, and the reaction mixture was allowed to stir at this temperature for 2 h. The reaction mixture was cooled and poured into a separatory funnel into which 10% Na_2CO_3 (50 mL, w/v) was added. The aqueous layer was removed and the organic layer was saved. The aqueous layer was then washed with EtOAc (3 × 30 mL), and the combined organic fraction was washed with H_2O (1 × 25 mL), dried (Na_2SO_4), and evaporated to 0.98 g (89%) of crude **8** as a dark oil. Purification by gradient flash column chromatography ($CHCl_3$/MeOH/NH_4OH, 95:5:1/90:10:1) yielded 0.59 g (55%) of pure **8** as the free base. The free base (0.48 g, 1.7 mmol) was dissolved in a minimal volume of 2-PrOH and was added to a solution of 0.21 g fumaric acid (1.8 mmol) in 2-PrOH. Addition of anhydrous ether resulted in crystalline **8**. Recrystallization in 2-PrOH gave 0.41 g (56%) of pure **8**, mp 136–141 °C. Note: if crystallization was difficult and the crude salt was dark, boiling in 2-PrOH with charcoal followed by filtration over Celite facilitated isolation of pure product.) IR (KBr, salt) 650 cm^{-1} (C-Cl); ^1H NMR ($CDCl_3$) δ 7.25 (d, J = 1.9 Hz, 1 H), 7.14 (dd, J = 6.3, 1.9 Hz, 1 H), 7.08 (d, J = 6.3 Hz, 1 H), 2.62 (s, 3 H); EIMS m/z 275, 277 (M + 2); $[\alpha]_D$ +19.6 (c 0.53, MeOH). Anal. ($C_{17}H_{22}NCl{\cdot}C_4H_4O_4{\cdot}2H_2O$) C, H, N.

(+)-3-Isothiocyanato-17-methylmorphinan Hydrochloride (9). A solution of **5** (0.52 g, 2.0 mmol, free base) in pentene-stabilized $CHCl_3$ (45 mL) was added to a solution of $NaHCO_3$ (0.64 g, 2.8 mmol) in H_2O (20 mL) at 0 °C.[20] The biphasic reaction mixture was allowed to stir under an atmosphere of argon, at 0 °C for 10 min. Freshly distilled thiophosgene (200 μL, 2.2 mmol) was added and the reaction mixture was allowed to stir at 0 °C for 10 min and room temperature for 30 min. The organic layer was removed, and the aqueous layer was extracted with $CHCl_3$ (2 × 20 mL). The combined organic fraction was washed with H_2O (1 × 20 mL), dried (Na_2SO_4), and evaporated to 0.60 g (98%) to an orange foam. The crude free base was dissolved in a minimal volume of 2-PrOH and acidified with a saturated solution of HCl in 2-PrOH (pH 4). Careful addition of anhydrous ether resulted in 0.59 g (88%) of crystalline **9**, mp 260 °C dec; IR ($CHCl_3$) 2160 cm^{-1} (br, NCS); CIMS m/z 299 (M + 1); HRMS (M^+) calcd for $C_{18}H_{22}N_2S$ 298.1504, found 298.1476; $[\alpha]_D$ +19.1 (c 0.68, MeOH). Anal. ($C_{18}H_{22}N_2S{\cdot}HCl{\cdot}^3/_4{\cdot}H_2O$) C, H, N.

(+)-(1-Phenyl-1*H*-5-tetrazolyl)-17-methylmorphinan (10). A modification of the procedure described by Reden et al.[21] was used beginning with the addition of 5-chloro-1-phenyl-1*H*-tetrazole (1.08 g, 6.0 mmol) and anhydrous K_2CO_3 (1.35 g, 9.8 mmol) to a solution of **1** (1.29 g, 5.0 mmol) in dry DMF (25 mL). The reaction mixture was allowed to stir at room temperature, under an atmosphere of argon, for 18 h. Extraction from H_2O (20 mL) with ether (3 × 20 mL) was followed by washing the combined ether fractions with 15% NaOH (1 × 15 mL) and then extracting the organic phase with 1 N HCl (3 × 20 mL). The ether layer was discarded, and the aqueous layer was neutralized with concentrated NH_4OH to pH 9, extracted with ether (3 × 20 mL), dried (Na_2SO_4), and evaporated to 1.65 g of a white glass (100%) that was homogeneous by TLC and was taken to the next step without further purification: IR ($CHCl_3$) 1660 (C=N), 1600 (Ar) cm^{-1}; ^1H NMR δ 7.50 (d, J = 8 Hz, 1 H), 7.47 (m, 2 H), 7.14 (m, 5 H), 2.37 (s, 3 H); CIMS m/z 402 (M + 1).

(+)-17-Methylmorphinan Fumarate (11). A modification of the procedure described by Reden et al.[21] was used to convert **10** to **11**. A mixture of **10** (1.55 g, 4.7 mmol) in glacial HOAc (40 mL) and 10% Pd/C (1.55 g) was hydrogenated (40 psig, 40 °C) for 96 h, when the reaction was determined to be complete by TLC (THF/hexane/NH_4OH, 1:1:0.1). The reaction mixture was filtered over Celite and evaporated to 1.16 g (100% crude) of a clear oil. Purification by flash column chromatography (THF/hexanes/NH_4OH, 1:1:0.1 to THF/NH_4OH, 9:1) afforded 0.60 g (53%) pure **11**, as the free base. The oily free base (0.30 g, 1.24 mmol) was dissolved in MeOH and added to a solution of fumaric acid (0.15 g, 1.24 mmol) in MeOH. The volatiles were removed in vacuo, and the salt was recrystallized in 2-PrOH/ether to give 0.30 g (68%) of **10**: HRMS (M^+) calcd for $C_{17}H_{23}N$ 241.1830, found 241.1825; $[\alpha]_D$ + 14.9 (c 1.15, MeOH).

(+)-3-Methoxymorphinan Hydrochloride (12). Compound **1** (7.4 g, 20 mmol) was converted to the free base by extraction from aqueous NH_4OH (20% v/v, 25 mL) into $CHCl_3$, followed by drying in vacuo. The crystalline free base was dissolved in freshly distilled (from P_2O_5) dichloroethane (65 mL); K_2CO_3 (11.0 g, 80 mmol) and ACE-Cl (11.4 g, 80 mmol) were added at 0 °C, under an atmosphere of argon.[22] The reaction mixture was warmed and allowed to stir at reflux for 6 h. Cooling was followed by filtration and removal of solvent in vacuo. The residue was dissolved in MeOH (60 mL) and allowed to stir at reflux for 1 h. Evaporation and recrystallization from EtOAc gave 5.29 g (90%) of pure **12**: mp 250 °C (lit.[42] mp 249–250.5 °C).

(+)-3-Hydroxy-17-formylmorphinan (13). Compound **12** (15.3 g, 52.2 mmol) was converted to the free base by extraction from aqueous NH_4OH (20% v/v, 100 mL) into $CHCl_3$, followed by drying in vacuo. The free base was dissolved in ethyl formate (200 mL) and formic acid (100%, 150 μL) was added. The reaction mixture was allowed to stir at reflux overnight. Evaporation gave the crude *N*-formyl-3-methoxymorphinan as a clear gum; TLC showed one major product spot, CIMS m/z 286 (M + 1). The intermediate gum was dissolved in CH_2Cl_2 (100 mL), and a solution of BBr_3 (20 mL, 209 mmol) in CH_2Cl_2 (500 mL) was added via addition funnel, over 10 min, at 0 °C, under an atmosphere of argon. Five minutes after the addition of BBr_3, the reaction was complete by TLC. The reaction mixture was poured onto a slurry of NH_4OH (100 mL, 400 g of ice) and stirred for 20 min. The reaction mixture was then poured into a separatory funnel, the organic phase was removed, and the aqueous phase was extracted with $CHCl_3$/MeOH (4:1, 3 × 100 mL). The combined organic phase was washed with H_2O (1 × 250 mL), dried (Na_2SO_4), and evaporated to 12.58 g (89%) of **13** as a white foam: IR ($CHCl_3$) 3260 (OH), 1650 (NCHO) cm^{-1}; ^1H NMR (showed rotamers) δ 8.15 (s, 1 H); 7.99 (s, 1 H); 6.94 (t, J = 6.2 Hz, 2 H); 6.81 (s, 1 H); 6.80 (s, 1 H); 6.69 (dd, J = 4.2, 8.4 Hz, 2 H); 6.26 (brs, 1 H); 6.24 (brs, 1 H); CIMS m/z 272 (M + 1).

Representative Procedure for O-Alkylation and Reduction. (+)-3-(2-Propoxy)-17-methylmorphinan Fumarate (15). A reaction mixture of **13** (3.0 g, 11 mmol), K_2CO_3 (7.7 g, 110 mmol), and 2-bromopropane (7.0 mL, 75 mmol) in dry DMF (15 mL) was allowed to stir at 60 °C overnight. The reaction mixture was cooled, filtered, diluted with H_2O (25 mL), and extracted with ether (3 × 25 mL). The ether layer was washed with H_2O (3 × 10 mL) and evaporated to a clear oil which was homogeneous by TLC and taken to the next step without further purification, CIMS m/z 314 (M + 1). A slurry of $LiAlH_4$ (1.60 g, 40 mmol) in dry THF (20 mL) was prepared in an argon-purged three-necked round-bottom flask, at 0 °C. The oily intermediate described above was dissolved in THF (10 mL) and added dropwise to the reaction mixture, under an atmosphere of argon. The ice bath was removed and the reaction was complete in 30 min. The reaction mixture was cooled to 0 °C and carefully quenched with H_2O (1.6 mL), aqueous NaOH (1.6 mL, 15% w/v), and H_2O (4.8 mL). The lithium salts were filtered and washed with ether. Evaporation of the filtrate and drying in vacuo gave 2.59 g (87%) of the free base of **15** as a clear oil. The free base was dissolved in MeOH and acidified with a solution of fumaric acid (1.0 g, 10 mmol) in MeOH, addition of ether resulted in 3.29 g (91%) of crystalline **15**: mp 181–185 °C; ^1H NMR ($CDCl_3$) δ 6.83 (m, 3 H), 4.56 (m, 1 H), 2.90 (s, 3 H), 1.28 (d, J = 3.1 Hz, 6 H); CIMS m/z 300 (M + 1); $[\alpha]_D$ +22.75 (c 1.09, MeOH). Anal. ($C_{20}H_{29}NO{\cdot}C_4H_4O_4$) C, H, N.

Biological Testing. Anticonvulsant Protocol. Male Sprague-Dawley rats (200–250 g; Zivic-Miller laboratories), n = 10 per group, were randomly assigned as control or drug-treated animals. Both groups were subjected to a single transauricular maximal electroshock (MES 2 s at 60 Hz and 50 mA) convulsion delivered through miniature alligator clips attached to the pinna of each ear. All compounds were administered subcutaneously (sc) and tested at 30 min, the time of peak anticonvulsant activity for 1.[4] All drugs were freshly prepared using appropriate dilutions

(42) Peet, N. P. N-Demethylation of Dextromethorphan *J. Pharm. Sci.* **1980**, *69*, 1447–1448.

in normal saline, except compound 9 which was dissolved in DMSO, and addition of HCl was necessary for dissolving compound 3. Injection volumes were 1–2 mL/kg. Control groups received an appropriate vehicle injection.

Binding Experiments. All binding experiments were carried out in 1-mL tubes (miniblocks, in a final incubation volume of 0.5 mL). All reagents were diluted and dispensed using TECAN and filtering was done using a Brandel M-48R. Samples were counted in 5 mL of Ecoscint A, after an extraction period of at least 6 h, using a Beckman LS 1701 liquid scintillation counter (with automatic corrections for quenching and efficiency). All compounds were dissolved in distilled H_2O except compound 3 which was dissolved in DMSO/lactic acid and diluted with distilled H_2O (final concentration each solvent, 0.01% at 10^{-5} M). Standards were obtained from commercial sources except dichlorokynurenic acid (DCK) which was a gift from Pfizer Central Research, Sandwich, Kent.

[^{3}H]Dextromethorphan ([^{3}H]1) Binding. Tissue Preparation. Frozen brains (male Sprague-Dawley rats or Dunkin Hartley guinea pigs, Charles River) were thawed, suspended in 10 volumes of ice-cold 0.32 M sucrose and homogenized using a polytron (30 s, setting 6). The suspension was then centrifuged at 1000*g* for 20 min and the pellet (P1) discarded. For the rat brain tissue preparation, the supernatant from the 1000*g* spin was centrifuged at 100000*g* for 60 min and the pellet resuspended in 2.5 volumes of 50 mM Tris-HCl (pH 7.4 at 25 °C) and frozen at −80 °C. Guinea pig brain subcellular fractions were prepared on the basis of the method of De Robertis et al.[43] The supernatant from the 1000*g* spin was first centrifuged at 40000*g* for 20 min. The pellet was resuspended in 10 volumes of ice-cold Tris-HCl and recentrifuged at 11500*g* for 20 min. This pellet (crude mitochondrial P_2) was washed once in Tris-HCl, resuspended in 2.5 volumes of Tris-HCl (as for rat brain) and frozen at −80 °C. The supernatant from the 20000*g* spin was centrifuged at 100000*g* for 60 min to give the microsomal pellet (P3). This was resuspended in 2 volumes of Tris-HCl (as above) and frozen at −80 °C.

Binding Assay. The method was based on one developed by Craviso and Musacchio.[26] [^{3}H]1 (50 μL, NEN, specific activity 85.3 Ci/mmol), at a final concentration of 5 nM, was incubated for 20 min at 23 °C with 400 μL of either rat or guinea pig brain membranes (approximately 0.3 mg of rat brain and guinea pig P_2 and 0.5 mg of guinea pig P_3) and 50 μL of buffer (to define total binding), cold 1 at 100 μM (to define nonspecific binding), or varying concentrations of displacing compound (10^{-9}–10^{-5} M). The reaction was terminated by dilution with ice-cold wash buffer (50 mM Tris-HCl, pH 7.4 at 0 °C, containing 100 mM choline chloride and 0.01% Triton X-100), followed by rapid filtration through GF/B filters presoaked >2 h in wash buffer (to reduce nonspecific binding of [^{3}H]1 to the filters). The filters were washed with 4 × 1 mL of wash buffer and counted as described above.

[^{3}H]TCP and [^{3}H]Glycine Binding. Tissue Preparation. The method was based on one developed by Bristow et al.[44] Frozen rat brains (minus cerebellum) were thawed and suspended in 10 volumes of ice-cold 0.32 M sucrose and homogenized using a Polytron (30 s, setting 6). The homogenate was then centrifuged at 1000*g* for 20 min, the pellet discarded and the supernatant centrifuged at 20000*g* for 20 min. The pellet from this was resuspended in 10 volumes of ice-cold distilled H_2O, vortexed and allowed to stand for 10 min before being centrifuged at 8000*g* for 20 min. The supernatant was then used to wash the buffy uppercoat away from the brown mitochondria-enriched pellet and centrifuged at 40000*g* for 20 min to give crude synaptic plasma membranes. These were washed twice in distilled H_2O and the pellets frozen at −20 °C for at least 18 h. They were then thawed and resuspended in 10 volumes of either 5 mM Tris-HCl (pH 7.4 at 0 °C) for the TCP assay or 50 mM Tris–acetate (pH 7.7 at 0 °C) for the glycine assay, vortexed, and washed a further 6 times by centrifuging at 40000*g* with a 10-min incubation at room temperature between each spin. The final pellet was resuspended in 2.5 volumes of either TCP buffer or glycine buffer, and frozen at −80 °C. On the day of the experiment, the tissue was thawed and washed once more in 4 volumes of the appropriate buffer before use in this assay.

[^{3}H]TCP Binding Assay. The method was a modification of one developed by Monahan et al.[45] [^{3}H]TCP (50 μL, NEN, specific activity 40.8 Ci/mmol), at a final concentration of 5 nM, was incubated for 60 min at 23 °C with 400 μL of rat brain crude synaptic plasma membranes prepared as described above (approximately 0.2 mg) and 50 μL of TCP buffer (for total binding), cold phencyclidine (PCP, for nonspecific binding), or varying concentrations of displacing compound (10^{-9}–10^{-5} M). The reaction was terminated by dilution with ice-cold wash buffer (5 mM Tris-HCl, pH 7.7 at 0 °C), followed by filtration through GF/B filters presoaked >2 h in 5 mM Tris-HCl containing 0.5% poly(ethylene imine) (PEI) to reduce filter binding. The filters were then washed with 4 × 1 mL of wash buffer and counted as described previously.

[^{3}H]Glycine Binding Assay. This method was modified from those employed by Bristow et al.[44] and Sacaan et al.[46] [^{3}H]Glycine (50 μL, NEN, specific activity 43 Ci/mmol), at a final concentration of 25 nM, was incubated for 15 min at 0 °C with 400 μL of rat brain crude synaptic plasma membranes and 50 μL of either glycine buffer (total binding), 1 mM D-serine (nonspecific binding), or varying concentrations of displacing compound (10^{-9}–10^{-5} M, except glycine which was tested from 10^{-8}–10^{-4} M). The reaction was terminated by dilution with ice-cold wash buffer (50 mM Tris-HCl, pH 7.7 at 0 °C) containing 10 mM $MgCl_2$ (to reduce dissociation of the ligand–receptor complex during the separation procedure), followed by rapid filtration through GF/B filters presoaked in Tris–acetate containing 0.1% PEI and 1 mM glycine (to reduce filter binding). The filters were then washed with 3 × 1 mL of wash buffer, and the filters were counted as before. The duration of the separation procedure was less than 6 s, and the reaction mixture and reagents were kept below 4 °C, to minimize dissociation of the fairly low affinity [^{3}H]glycine from its binding site.

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