Bicyclic Hydantoins with a Bridgehead Nitrogen. Comparison of Anticonvulsant Activities with Binding to the Neuronal Voltage-Dependent Sodium Channel

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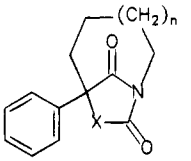
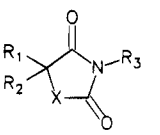
The anticonvulsant activity of diphenylhydantoin (DPH or phenytoin) is consistent with its actions on the neuronal voltage-dependent sodium channel. To further elucidate the binding requirements for this site, we synthesized several hydantoin analogs and evaluated these in in vitro sodium channel-binding and/or in vivo whole animal anticonvulsant assays. 5-Pentyl-5-phenylhydantoin (**8**), the most potent binder to the sodium channel in this study, had the same affinity as DPH (IC_{50} = 40 μM), revealing that one phenyl ring is sufficient for good interactions. Since our previous studies with monophenyl-substituted bicyclic 2,4-oxazolidinediones suggested that N3-alkylation and the conformational constraint of a 5-alkyl substituent over one face of the oxazolidinedione ring improved activity, we synthesized two examples of analogous bicyclic hydantoins. However, the bicyclic hydantoins were much less potent binders to the neuronal voltage-dependent sodium channel than their monocyclic counterparts. The binding activity for the more potent bicyclic hydantoin, 1,8-diaza-9,10-dioxo-7-phenylbicyclo[5.2.1]decane (**4**) (IC_{50} = 427 μM), was comparable to that of the ring-opened, N3-methylated monocyclic hydantoin model, 5-butyl-3-methyl-5-phenylhydantoin (**9**) (IC_{50} = 285 μM), and these were 8–11 times less potent than the monocyclic model **8**, which contains a free imide NH. Furthermore, 5-butyl-5-phenylhydantoin (**7**; IC_{50} = 103 μM) was less potent than **8**, suggesting that increased log *P* may enhance binding. Thus, *unlike* 2,4-oxazolidinediones, N3-alkylation of hydantoins dramatically decreases sodium channel-binding activity. Bicyclic hydantoin **4** was nevertheless a good anti-MES anticonvulsant in mice (ED_{50} = 86 mg/kg), although this activity likely results from mechanisms other than interactions at the neuronal voltage-dependent sodium channel. Compound **4** was also relatively neurotoxic (TD_{50} = 124 mg/kg). These results suggest that the binding of hydantoins to the sodium channel may be enhanced by (a) a free imide NH group and (b) an increased log *P*. Furthermore, 2,4-oxazolidinediones and hydantoins must either orient differently in the same binding site or interact with different sites on the neuronal voltage-dependent sodium channel.

We have been interested in the preparation of bicyclic imides with structures **1**–**4** as probes of cyclic imide anticonvulsant-binding sites. These compounds were first proposed by Edward E. Smissman,[1] and we named them "smissmanones" upon reporting the first successful synthesis of examples from this class.[2]

The neuronal voltage-dependent sodium channel is a putative site of action for the antimaximal electroshock (anti-MES) anticonvulsants diphenylhydantoin (DPH or phenytoin, Figure 1; a cyclic imide) and carbamazepine (which contains an acyclic urea side chain).[3,4] These agents bind to the sodium channel at therapeutically relevant concentrations. Such binding is voltage- and frequency-dependent, providing a consistent explanation for selective effects on hyperactive versus normal neurons. Unfortunately, this binding site is not well characterized, although compounds which bind with enhanced potency and selectivity may provide better anti-MES anticonvulsants.





	n	X
1	1	O
2	2	O
3	1	NH
4	2	NH

	X	R_1	R_2	R_3
trimethodione	O	CH_3	CH_3	CH_3
phenytoin	NH	Ph	Ph	H
5	O	Ph	C_2H_5	CH_3
6	NH	Ph	n-C_3H_7	H
7	NH	Ph	n-C_4H_9	H
8	NH	Ph	n-C_5H_{11}	H
9	NH	Ph	n-C_4H_9	CH_3

Figure 1. Structures for the cyclic imides discussed in this study.

We have utilized smissmanones as part of a study to delineate structural features on cyclic imides which result in tight binding. We previously reported the syntheses[2] and the anticonvulsant and sodium channel-binding activities[5] for bicyclic 2,4-oxazolidinediones **1**

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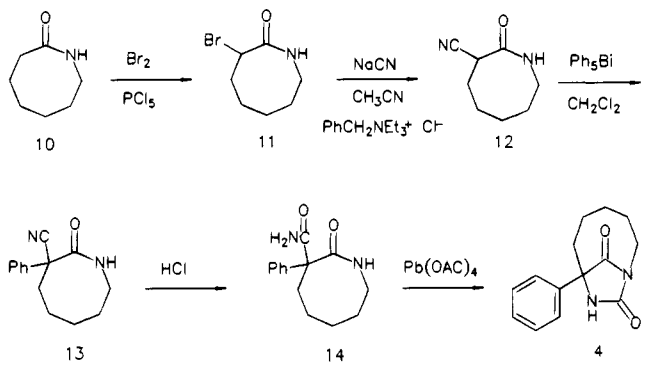
Scheme 1



and **2** and the monocyclic model **5**. We have also reported the synthesis of bicyclic hydantoin **3**.[6] Here we describe the synthesis of bicyclic hydantoin **4**, and we present new sodium channel-binding and whole animal anticonvulsant activities for bicyclic hydantoins **3** and **4** which permit comparisons with the bicyclic 2,4-oxazolidinediones. Additionally, trends in sodium channel-binding activities for homologous hydantoins are discussed with regard to effects of structure versus log *P* on binding.

Chemistry

The syntheses of compounds **1**,[2] **2**,[2] **3**,[6] **5**,[5] and **6**[7] are previously described. Hydantoins **7** and **8** were prepared according to a literature method[8] from commercially available valerophenone and hexanophenone, respectively, using the Bucherer–Bergs reaction. Methylation[9] of the imide nitrogen in **7** using NaOH and dimethyl sulfate gave previously reported **9**[10] in 87% yield.

The synthesis of bicyclic hydantoin **4** was based upon the approach[6] that we developed for preparing **3** and is summarized in Scheme 1. In this 8-membered ring system, experimental procedures were essentially the same as those utilized previously in the 7-membered ring system involved in the synthesis of **3**. One exception is the conversion of bromolactam **11**, prepared by the monobromination of lactam **10** in 40% yield (according to a published procedure[11]), to cyanolactam **12**. During the synthesis of **3**,[6] this step was accomplished in 55% yield by treating α-bromocaprolactam with NaCN and 18-crown-6 in CH_3CN. However, the treatment of **11** under identical conditions resulted exclusively in elimination to provide the α,β-unsaturated lactam. This behavior was also observed by others who reported[12] that the treatment of **11** with cyanide in EtOH, DMF, or DMSO under a variety of conditions failed to produce any nitrile **12**. After a number of trials using differing conditions of cyanide salt, solvent, and catalyst, we found that treating **11** with NaCN and $PhCH_2NEt_3^+Cl^-$ in CH_3CN provided **12** in 50% isolated yield. Lactam **12** then underwent α-phenylation using Ph_5Bi in essentially quantitative yield (as compared to 74% yield for the 7-membered ring procedure). The nitrile **13** was hydrolyzed to the amide **14** (91% yield), and this was cyclized upon treatment with $Pb(OAc)_4$ via an intramolecular N-alkylation of the intermediate isocyanate to provide **4** in 67% yield (as contrasted to 48% yield for the comparable cyclization which produced **3**).

Results and Discussion

While the widely prescribed cyclic imide anticonvulsant diphenylhydantoin (Figure 1) interacts well with the sodium channel, other common cyclic imide anticonvulsants such as barbiturates and 2,4-oxazolidinediones (e.g., trimethadione in Figure 1) are poor binders. However, our previous biological studies[5] with 2,4-oxazolidinediones demonstrated that 5-alkyl-5-phenyl-2,4-oxazolidinediones exhibited both anti-MES and modest sodium channel-binding activities. Furthermore, the sodium channel-binding activity of this class was moderately enhanced by methylation of the imide nitrogen to give **5** (Figure 1 and Table 2), although this activity was judged insufficient to account for the moderate anti-MES effect. As summarized in Table 2, the greatest improvement in sodium channel-binding activity for the 2,4-oxazolidinediones resulted from incorporation of the *N*-methyl and 5-alkyl substituents into a ring to provide **2**, which was a good anti-MES anticonvulsant (ED_{50} = 66 mg/kg) that was also a relatively good binder to the sodium channel (IC_{50} = 160 μM). Since diphenylhydantoin (see Table 2) is a more potent anti-MES anticonvulsant (ED_{50} = 10 mg/kg) and a better sodium channel binder (IC_{50} = 40 μM) than **2**, we proposed that bicyclic hydantoin derivatives **3** and **4**, as was found for 1 and **2**, may provide better anti-MES and sodium channel binding activities than monocyclic hydantoins.

Table 1. Selected Data for Compounds 4 and 12–14[a]

compd	isolated yield, %	mp, °C (recrys solv)	^{1}H NMR ($CDCl_3$, δ)	^{13}C NMR ($CDCl_3$, δ)	IR,[b] cm^{-1} (C=O)
4	67	151–152 (EtOAc/hexane)	7.6–7.3 (m, 5H, Ph), 6.2 (bs, 1H, NH), 4.0–3.6 (m, 2H, NCH_2), 2.6–2.5 (m, 1H, CH_2), 2.4–1.2 (m, 7H, CH_2)	24.6, 33.4, 41.5, 45.6, 67.5, 126.1, 128.4, 135.9, 159.7, 179.6	1705, 1765
12	50	164–166 (EtOAc)	7.0 (bs, 1H, NH), 3.9 (t, 1H, CHCN), 3.5–3.1 (m, 2H, NCH_2), 2.2–2.0 (m, 2H, CH_2), 1.8–1.4 (m, 6H, CH_2)	24.2, 24.3, 31.7, 33.5, 34.0, 42.3, 76.6, 77.0, 77.4, 118.0, 169.3	1670 (2270, CN)
13	100	oil[c]	7.6–7.3 (m, 5H, Ph), 6.3 (bs, 1H, NH), 3.5–3.1 (m, 2H, NCH_2), 2.9–2.3 (m, 2H, CH_2CPh), 2.2–1.4 (m, 6H, CH_2)	22.0, 23.0, 30.0, 38.9, 40.4, 54.5, 120.3, 126.5, 128.7, 129.0, 129.3, 171.4	1655 (2270, CN)
14[d]	91	121–123 (EtOAc/hexane)	7.4–7.2 (m, 6H, Ph + NH), 6.0–5.7 (m, 2H, NH_2), 3.2–2.6 (m, 2H, NCH_2), 2.6–2.4 (m, 1H, CH_2), 2.1–1.3 (m, 7H, CH_2)	23.5, 23.8, 30.0, 37.7, 62.1, 126.3, 127.1, 127.6, 140.5, 172.8, 176.3	1620–1680 (broad)

[a] All compounds were also analyzed by (1) GC/MS (EI, 70 eV), giving one peak in the GC and the expected molecular ion peak, and (2) elemental analyses for C, H, N (within ±0.3% of calculated values, except for **13**; see footnote c). [b] Compounds **12** and **14** were recorded in KBr; compound **4** was recorded in mineral oil; compound **13** was recorded as a thin film. [c] Purified by flash chromatography on silica gel ($CHCl_3$): R_f 0.51 (silica gel; 5% MeOH/$CHCl_3$). Anal. ($C_{14}H_{16}N_2O \cdot {}^3/_4H_2O$) C, N; H: calcd, 7.29; found 6.61. [d] ^{13}C NMR recorded at 100 °C in DMSO-d_6 due to upfield peak broadening at room temperature.

Table 2. Sodium Channel-Binding and Anticonvulsant Activities

			anticonvulsant (mice ip)					
			phase I (best activity, mg/kg)[a]			phase II		
compd	log P[b]	Na^+ channel IC_{50} (μM)	MES	scMet	rotorod	time (h)	MES ED_{50} (mg/kg)	rotorod TD_{50} (mg/kg)
1[c]	2.65	380	>300	300 (1/1)	>300			
2[c]	3.05	160	100 (3/3)[d]	100 (1/1)	100 (8/8)	0.25	66 [51–84][e]	147 [93–226]
3	2.01	700	100 (3/3)	100 (3/4)	300 (4/4)			
4	2.51	427[f] (376–484)[g]	100 (3/3)	>300	300 (4/4)	0.25	86 [68–96]	124 [107–149]
5[c]	2.65	500	300 (1/1)	30 (1/1)	300 (1/4)	0.5	124 [104–139]	504 [437–558]
6[h]	1.96	162 (136–193)	30 (1/1)	100 (4/4)	100 (4/4)	1.0	25 [22–28]	85 [80–90]
7	2.46	103 (85–124)						
8	2.96	39 (32–47)						
9	3.01	285 (232–350)						
14		*i*	100 (1/3)	300 (4/4)	300 (4/4)			
DPH[j]	2.46[k]	40[l]				2.0	10 [8–10]	66 [52–72]
TMD[m]	−0.37[n]	>1000[l]				1.0	627 [538–705]	819 [652–1096]

[a] Concentration of test compound used in assay. All anticonvulsant and toxicity assays were performed 30 min after test compound administration. [b] Calculated using parent structure log P values in ref 13 and π values for substituents in ref 14 (see Results and Discussion). [c] Data taken from ref 5. [d] Number of animals protected or toxic compared to number tested. [e] Numbers in brackets are 95% confidence intervals. [f] Other in vitro mechanism-related assays were performed for **4** in phase Va: (1) benzodiazepine receptor (ligand = [^{3}H]flunitrazepam at 10 nM; tissue = mouse whole brain P_2 pellet), no inhibition up to 100 μM **4**; (2) GABA receptor (ligand = [^{3}H]GABA at 50 nM; tissue = mouse whole brain P_2 pellet), no inhibition up to 10 μM **4**; (3) adenosine uptake (ligand = [^{3}H]adenosine at 1 μM; tissue = mouse whole brain synaptosomes), no inhibition up to 100 μM **4**. [g] Range describing −1 to +1 standard deviation. [h] Anticonvulsant data taken from ref 7. The sodium channel value was determined in the present study. [i] 33% inhibition at 500 μM. [j] Anticonvulsant data taken from ref 15. [k] log P taken from ref 13. [l] References 3 and 4. [m] TMD = trimethadione. Anticonvulsant data taken from ref 15. [n] log P taken from ref 14.

As part of the present study on hydantoins, we also evaluated the sodium channel-binding activity of compound **7**, a monocyclic model for bicyclic hydantoin **3**. Similarly, hydantoins **8** and **9** also represent ring-opened analogs of bicyclic hydantoin **4**, but each results from a different disconnection along the alkyl bridge. As shown in Table 2, the IC_{50} obtained for **8** in the sodium channel-binding assay was nearly identical to that reported for DPH, revealing that appropriately substituted 5-alkyl-5-phenylhydantoins, like DPH, may interact efficiently with the sodium channel.

We were thus encouraged by the proposition that, as observed for the 2,4-oxazolidinediones, incorporation of the 5-alkyl substituents of **7** and **8** into a bicyclic structure (**3** and **4**) might further enhance sodium channel-binding activity in the hydantoin series. However, as shown in Table 2, the opposite effect was observed. While bicyclic hydantoin **4**, which contains the larger alkyl bridge, was a better binder than **3**, this activity remained 11-fold less potent than that seen for monocyclic model **8**.

Comparisons of the sodium channel-binding activities for homologous pairs of compounds (e.g., **1** vs **2**,; **3** vs **4**, **7** vs **8**) in Table 2 revealed that the larger compounds were consistently more potent binders, suggesting that partition coefficients (P) may be important. We also determined in the present study the sodium channel-binding affinity for hydantoin **6**, which we evaluated previously,[7] and found that the results were consistent with the above trend. We thus estimated the log P values for the compounds in Table 2 using reported (experimentally measured)[13] log P values for the parent structures, 5-phenyl-2,4-oxazolidinedione (log P = 1.09) and 5-phenylhydantoin (log P = 0.46), to which were added the appropriate π values for C5 and N3 substituents to provide the final log P. The π values used were 0.5 for each CH_2 or CH_3 in the alkyl chain at C5[14] and 0.56 for an N-CH_3 substituent.[14] The extra ring closure in bicyclic compounds **1**–**4** was treated as a contribution of −0.5.[13] For example, the log P for hydantoin **9** was calculated as log $P_{parent} + \pi_{5\text{-butyl}} + \pi_{N\text{-Me}} = 0.46 + 2.0 + 0.56 = 3.01$. Since the ring closure of **9** provides bicyclic hydantoin **4**, the log P of **4** was calculated as $\log P_9 + \pi_{ring\ closure} = 3.01 + (-0.5) = 2.51$. Log P values for all other compounds in Table 2 were estimated in a similar fashion.

Since changes in log P corresponded with changes in IC_{50} in the sodium channel-binding assay, a comparison was made between different structures with similar log P values to provide insight into structural requirements other than log P that are important for the binding of hydantoins to this site. Hydantoins **8** and **9** have essentially the same lipophilicity, but **8** is 7 times more potent, revealing that a free imide NH group is necessary for optimum activity. This conclusion is further supported by the observation that hydantoin **9**, which is more lipophilic than **7** but contains an N-methyl group, is 2 times less potent in binding to the sodium channel. Finally, N3-alkylated monocyclic hydantoin **9** is more lipophilic and a more potent binder to the sodium channel than the analogous N3-alkylated bicyclic hydantoin **4**, revealing that, unlike 2,4-oxazolidinediones, conformational restriction of the 5-alkyl group across one face of the cyclic imide ring has little effect on sodium channel-binding potency.

Several compounds in Table 2 were also evaluated for their whole animal anticonvulsant effects in mice. Of particular relevance to this study were the observations

that bicyclic hydantoins **3** and **4**, which are poor binders to the sodium channel, both possessed relatively good anti-MES anticonvulsant activities. This activity for **4** was quantitated, providing an anti-MES ED_{50} of 86 mg/kg. Unfortunately, toxicity in the rotorod assay was nearly as great (TD_{50} = 124 mg/kg), revealing a poor therapeutic ratio. Since the anti-MES activity of **4** must not result from the modest sodium channel-binding activity, other potential mechanisms of action were investigated. Phase V evaluation revealed an ED_{50} (114 mg/kg) against seizures induced by subcutaneous bicuculline (a $GABA_A$ antagonist) that was nearly as potent as the anti-MES effect, suggesting that the mechanism of action may involve the GABA system. In vitro radioligand-binding assays in phase Va using [^{3}H]-flunitrazepam (a benzodiazepine receptor agonist) and [^{3}H]GABA, as well as studies on [^{3}H]adenosine uptake, revealed no significant effects.

In summary, 5-alkyl 5-phenyl-substituted monocyclic hydantoins may bind efficiently to the sodium channel. The above studies suggest that the binding of these hydantoins to the sodium channel is enhanced by (a) an increased log *P* and (b) a free imide NH group. In contrast to 5-alkyl-5-phenyl-2,4-oxazolidinediones, alkylation of the hydantoin imide nitrogen with a methyl group or the presence of a bridging 5-alkyl substituent across one face of the hydantoin ring, as in smissmanones **3** and **4**, diminishes sodium channel-binding activity. Thus 2,4-oxazolidinediones and hydantoins must either orient differently at a single site or interact with different sites on the neuronal voltage-dependent sodium channel.

Experimental Section

Hydantoins **7** and **8** were prepared from valerophenone and hexanophenone, respectively, via a Bucherer–Bergs reaction as previously described.[8] Hydantoin **7** underwent N3-methylation[9] using NaOH and Me_2SO_4 to give **9**.[10]

Except for the conversion of **11** to **12**, the synthetic procedures for preparing smissmanone **4**, as summarized in Scheme 1, were essentially identical to those reported[6] for the preparation of **3**. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ at ambient temperature on a GE 300 FT NMR spectrometer (300.1 MHz for ^{1}H). IR spectra were recorded on a Beckman Acculab-1 spectrometer, and elemental analyses were performed by Atlantic Microlabs of Atlanta, GA.

[^{3}H]Batrachatoxinin A 20-α-benzoate ([^{3}H]BTX-B) with a specific activity of 30 Ci/mmol was obtained from New England Nuclear (Boston, MA).

Hexahydroazocin-2(1*H*)-one-3-carbonitrile (12). A mixture of bromolactam **11** (2.7 g, 0.013 mol), powdered NaCN (3.0 g, 0.061 mol), and benzyltrimethylammonium chloride (3.9 g, 0.021 mol) in anhydrous acetonitrile (25 mL) was heated at reflux with stirring for 30 h. This was concentrated to dryness on a rotary evaporator, and EtOAc (50 mL) was added to the crystalline residue. The mixture was stirred and heated at reflux for 20 min and filtered, and the filter washed with additional hot EtOAc (75 mL). The filtrate was concentrated, and the residue was chromatographed on a flash silica gel column (2.5 × 20 cm; 10:10:1 $CHCl_3$/Et_2O/EtOH). The appropriate fractions were combined and concentrated to give **12** (1.0 g, 50%) as a white solid: mp 164–166 °C (EtOAc).

Sodium Channel-Binding Assay. We previously reported the details of this procedure.[5] Briefly, synaptoneurosomes (~1 mg of protein) from rat cerebral cortex were incubated for 40 min at 25 °C with the test compound (seven different concentrations spanning the IC_{50}) in a total volume of 320 μL containing 10 nM [^{3}H]BTX-B and 50 μg/mL scorpion venom. Incubations were terminated by dilution with ice cold buffer and filtration through a Whatman GF/C filter paper, and the filters were washed three times with ice cold buffer. Filters were counted in a Beckman scintillation counter. Specific binding was determined by subtracting the nonspecific binding, which was measured in the presence of 300 μM veratridine, from the total binding of [^{3}H]BTX-B. All experiments were performed in triplicate and included a control tube containing 40 μM DPH. The IC_{50} values were determined from a Probit analysis of the dose–response curve and excluded doses producing less than 10% or greater than 90% inhibition.

Anticonvulsant Assays. All whole animal anticonvulsant and neurotoxicity assays were conducted by the Antiepileptic Drug Development Program of the Epilepsy Branch, National Institute of Neurological Disorders and Stroke. A description of this testing program along with the protocols employed has been published.[15] Briefly, phases I and II employ ip administration in mice for two anticonvulsant assays, a maximal electroshock test, and a subcutaneous metrazol (scMet) test, and a rotorod toxicity test. Phase I is a preliminary qualitative assay, and selected compounds from phase I undergo quantification of activities (ED_{50} and TD_{50}) in phase II. Phase V involves anticonvulsant drug differentiation in mice (ip) and consists of an in vitro portion and an in vivo portion. The latter evaluates activity against seizures induced by subcutaneous bicuculline, picrotoxin, and strychnine, since each of these convulsants acts by a somewhat different mechanism. Bicuculline and picrotoxin bind to different sites on the $GABA_A$ receptor, while strychnine acts at the glycine receptor. The in vitro portion consists of radioligand receptor-binding assays in phase Va using crude whole mouse brain synaptic membranes[16] for benzodiazepine receptor binding (employing [^{3}H]-flunitrazepam, a benzodiazepine receptor agonist)[17] and γ-aminobutyric acid receptor binding (employing [^{3}H]GABA).[18,19] Additionally, phase Va includes adenosine uptake studies in mouse whole brain synaptosomes (employing [^{3}H]adenosine).[20]

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