Synthesis and Anticonvulsant Activity of 2-Iminohydantoins

Chul-Hoon Kwon,* Muhammad Tahir Iqbal, and John N. D. Wurpel

Department of Pharmaceutical Sciences, College of Pharmacy and Allied Health Professions, St. John's University, Jamaica, New York 11439. *Received July 23, 1990*

Iminohydantoins selectively substituted at position C-5 and their 1-carbobenzoxy derivatives have been synthesized, and their anticonvulsant activity was evaluated in mice. In general, the more lipophilic 1-carbobenzoxy iminohydantoins were more potent than the unsubstituted counterparts. Evaluation of the individual enantiomers of the chiral iminohydantoins showed that the anticonvulsant activity resided primarily in the *S* isomers. In this study, (*S*)-(+)-1-carbobenzoxy-5-isobutyl-2-iminohydantoin (**9a**) was the most active member. This compound was not nearly as active as phenytoin against electrically induced convulsions, but was also active against pentylenetetrazole-induced seizures, suggesting a broader clinical potential. The closest analogue of phenytoin, viz., 5,5-diphenyl-2-iminohydantoin (1), failed to show any significant activity. Methylation on N-3 or the imino nitrogen of 1 also did not provide a compound with substantial activity. 2-Thiophenytoin was not active against electroshock seizures and showed only a weak activity against pentylenetetrazole. This study suggested that the structure–activity relationship of 2-iminohydantoins was quite different from that of 2-hydantoins.

Epilepsy is a collective designation of seizure disorders that affect over two million Americans.[1,2] Currently marketed anticonvulsants do not often provide complete control of seizures, and are associated with a wide range of side effects. A need currently exists for improved anticonvulsant drugs.

The use of hydantoins as antiepileptic drugs was initially introduced by Sobotka[3] and then by Merritt and Putnam.[4] Since their introduction, the effect of structural modification of the hydantoin ring on anticonvulsant activity has been a subject of great interest and the structure–activity relationship (SAR) has been discussed.[5-7] In general, the 5-phenylhydantoins suppress electrically induced convulsions in experimental animals (supramaximal electroshock seizure test, MES test) but are ineffective against chemically induced convulsions (subcutaneous Metrazol seizure test, scMET test).[8] Phenytoin (5,5-diphenylhydantoin, DPH, Dilantin), the most active member in this class, is one of the most widely used anticonvulsant agents, but is associated with a variety of toxic effects[9] and is teratogenic.[10]

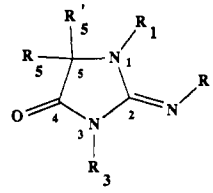
In contrast to the hydantoins, there have been relatively fewer studies on the sulfur analogues, viz., 2-thiohydantoins. There are conflicting reports on the anticonvulsant activity of 2-thiophenytoin (5,5-diphenyl-2-thiohydantoin, DPTH), the closest analogue of phenytoin. Knofel and Lehman reported[11] that 2-thiophenytoin did not raise the threshold of electrically induced convulsions in cats. Later studies, however, indicated that 2-thiophenytoin protected against maximal electroshock seizures in rats.[12,13] Limited information on the SAR of 2-thiohydantoins is available, and the SAR is quite different from that of the hydantoin series: 2-thiophenytoin was not the most active member in this series and 5-phenyl-5-alkyl-2-thiohydantoin derivatives were also found to have weak or no anticonvulsive activity.[11] On the other hand, 2-thiohydantoins with a four carbon alkyl chain at the C-5 carbon, and a two to three carbon alkyl chain at the N-3 nitrogen were the most active, especially against scMET test.[14] In general, and in contrast to active hydantoins, the 2-thiohydantoins were more effective against scMET test than against MES test. Despite the potent anticonvulsive activities exhibited by some of the 2-thiohydantoins, further development of 2-thiohydantoins as clinically useful anticonvulsants was hampered by their notable antithyroidal properties, which were attributed to the structural similarity between the 2-thiohydantoins and the thiouracils, well-known antithyroid drugs.[14-17]

Another structurally close analogue of hydantoin is 2-iminohydantoin (glycocyamidine). The phenytoin analogue, viz., 5,5-diphenyl-2-iminohydantoin (1), is a known compound;[18] however, its biological activity has not been reported. The only available information on anticonvulsant activity of iminohydantoins is that 3-[β-(diethylamino)ethyl] and 3-(β-morpholinoethyl) derivatives of 5,5-diphenyl-2-iminohydantoin showed some activity against scMET test, but not against MES test.[19]

The close structural resemblance among the three types of hydantoins, viz., 2-iminohydantoins, 2-thiohydantoins,

(1) Lennox, W. G.; Lennox, M. A. *Epilepsy and Related Disorders*; Little, Brown and Co.: Boston, 1960; Vol. I.
(2) Church, J.; Davies, S. N.; Lodge, D. *Neurol. Neurobiol.* **1987**, *24*, 115.
(3) Sobotka, H.; Holzman, M. F.; Kahn, J. *J. Am. Chem. Soc.* **1932**, *54*, 687.
(4) (a) Merritt, H. H.; Putnam, T. J. *Arch. Neurol. Psychiatry* **1938**, *39*, 1003. (b) Merritt, H. H.; Putnam, T. J. *J. Am. Med. Assoc.* **1938**, *111*, 1068.
(5) Jones, G. L.; Woodbury, D. M. *Drug Dev. Res.* **1982**, *2*, 333.
(6) Poupaert, J. H.; Vandervorst, D.; Guiot, P.; Moustafa, M. M. M.; Dumont, P. *J. Med. Chem.* **1984**, *27*, 76.
(7) Cortes, S.; Liao, Z.-K.; Watson, D.; Kohn, H. *J. Med. Chem.* **1985**, *28*, 601.
(8) Krall, R. L.; Penry, J. K.; White, B. G.; Kupfergerg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409.
(9) (a) Rall, T. W.; Schleifer, L. S. Drugs Effective in The Therapy of Epilepsies. In *The Pharmacological Basis of Therapeutics*, 7th ed.; Goodman and Gilman's, Eds.; Macmillan Publishing Company: New York, 1985; pp 446–472. (b) Earnest, M. P.; Marx, J. A. *JAMA* **1983**, *249*, 762. (c) Hassell, T. M.; Gilbert, G. H. *Am. J. Pathol.* **1983**, *112*, 218. (d) Keith, D. A.; Gundberg, C. M.; Japour, A.; Aronoff, J.; Alvarez, N.; Gallop, P. M. *Clin. Pharmacol. Ther.* **1983**, *34*, 529.
(10) (a) Harbison, R. D.; Becker, B. A. *Teratology* **1969**, *2*, 305. (b) Massey, K. M. *J. Oral Ther. Pharmacol.* **1966**, *2*, 380. (c) Monson, R. R.; Rosenberg, L.; Hartz, S. C.; Shapiro, S.; Heinonen, O. P.; Slone, D. *N. Engl. J. Med.* **1973**, *289*, 1049–1052. (d) Hanson, J. W.; Myrainthipoulous, N. C.; Harvey, M. A. S.; Smith, D. W. *J. Pediatr.* **1976**, *89*, 662. (e) Finnell, R. H. *Science* **1981**, *211*, 483. (f) Estus, S.; Blumer, J. L. *J. Pharmacol. Exp. Ther.* **1989**, *251*, 782.
(11) Knoefel, P. K.; Lehmann, G. *J. Pharmacol. Exp. Ther.* **1942**, *76*, 194.
(12) Raines, A.; Standaert, F. G. *Epilepsia* **1969**, *10*, 211.
(13) Sohn, Y. I.; Levitt, B.; Raines, A. *Arch. Intern. Pharmacodyn.* **1970**, *188*, 284.
(14) Gesler, R. M.; Lints, C. E.; Swinyard, E. A. *Toxicol. Appl. Pharmacol.* **1961**, *3*, 107.
(15) Marx, J. V.; Richert, D. A.; Westerfeld, W. W. *J. Med. Chem.* **1970**, *13*, 1179.
(16) Marx, J. V.; Richert, D. A.; Westerfeld, W. W.; Ruegamer, W. R. *Biochem. Pharmacol.* **1971**, *20*, 3009.
(17) Mehlman, M. A.; Tobin, R. B.; Ruegamer, W. R.; Madappally, M. W. *Biochem. Pharmacol.* **1972**, *21*, 2031.
(18) Hoffmann, C. *Bull. Soc. Chim. Fr.* **1950**, 659.
(19) Lempert, K.; Breuer, J.; Lempert-Streter, M.; Pataky, I.; Pfeifer, K. *Magyar. Kem. Folyoirat.* **1959**, *65*, 110.

0022-2623/91/1834-1845$02.50/0



compound	R	R_1	R_3	R_5	R'_5
1	-H	-H	-H	$-C_6H_5$	$-C_6H_5$
2	-H	-H	-H	$-C_6H_5$	-H
3	-H	-H	-H	$-CH_2C_6H_5$	-H
4	-H	-H	-H	$-CH_2CH(CH_3)_2$	-H
5	-H	-H	-H	-H	-H
6	-H	$-(C=O)OCH_2C_6H_5$	-H	$-C_6H_5$	$-C_6H_5$
7	-H	$-(C=O)OCH_2C_6H_5$	-H	$-C_6H_5$	-H
8	-H	$-(C=O)OCH_2C_6H_5$	-H	$-CH_2C_6H_5$	-H
9	-H	$-(C=O)OCH_2C_6H_5$	-H	$-CH_2CH(CH_3)_2$	-H
10	-H	$-(C=O)OCH_2C_6H_5$	-H	-H	-H
11	$-CH_3$	-H	-H	$-C_6H_5$	$-C_6H_5$
12	-H	-H	$-CH_3$	$-C_6H_5$	$-C_6H_5$

Figure 1.

and hydantoins, and that the latter two are well-established anticonvulsants warranted exploration of 2-iminohydantoins as potential anticonvulsants.

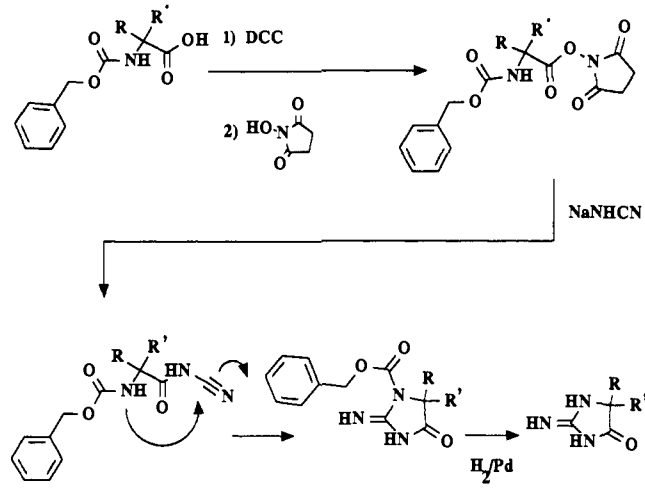
In this study, we have focused primarily on the substituent effect at C-5 of the 2-iminohydantoin ring, and the compounds selected were 5,5-diphenyl-2-iminohydantoin (**1**), 5-phenyl-2-iminohydantoin (**2**), 5-benzyl-2-iminohydantoin (**3**), 5-isobutyl-2-iminohydantoin (**4**), 2-iminohydantoin (**5**), and their 1-carbobenzoxy derivatives **6**, **7**, **8**, **9**, and **10**, respectively, to enhance lipophilicity of the corresponding 2-iminohydantoins (Figure 1). In addition, *N*-methyl-5,5-diphenyl-2-iminohydantoin (**11**) and 3-methyl-5,5-diphenyl-2-iminohydantoin (**12**) were also included to study the effect on modulation of hydrogen-bonding capability of **1**. Phenytoin served as positive control and 2-thiophenytoin was included as comparison purpose.

Chemistry

The 1-carbobenzoxy-5-substituted-2-iminohydantoins were prepared essentially by the methods[20] published previously with some modifications. Commercially available carbobenzoxy (*Z*) amino acids were used as the starting materials except for the compounds **6** and **7** where the corresponding amino acids were coupled with benzyl chloroformate to produce the *N*-carbobenzoxy amino acids. The acylation of 2,2-diphenylglycine required an additional equivalent of benzyl chloroformate presumably due to the steric hindrance provided by the two bulky phenyl rings on the molecule. *N*-Carbobenzoxy-protected amino acid was allowed to react initially with dicyclohexylcarbodiimide (DCC) and then with *N*-hydroxysuccinimide to form activated succinimide ester. The succinimide ester was coupled with excess sodium cyanamide (or with cyanamide and NaOH) to initially produce *N*-carbobenzoxy-α-aminoacylcyanamide sodium salt, as indicated by the presence of a band typically at 2140 cm^{-1} ($-N=C=N^-$) of its IR spectrum. The reaction mixture was acidified and extracted with a suitable organic solvent to obtain the un-ionized N-protected aminoacylcyanamide, as indicated by the presence of an IR band typically at 2260 cm^{-1} ($-NHC\equiv N$). This tautomeric relationship between

(20) Kwon, C.-H.; Nagasawa, H. T. *Synth. Commun.* **1987**, *17*, 1677.

Scheme I



carbodiimide and cyanamide of acylcyanamides has been previously reported.[21] The crude N-protected aminoacylcyanamide underwent intramolecular cyclization spontaneously or by heat treatment to the corresponding N^1-protected 2-iminohydantoin in good yields. Removal of the carbobenzoxy group was effected by hydrogenation to produce the corresponding 2-iminohydantoin in 20–50% yields (Scheme I). This procedure afforded synthesis of optically active isomers of some of the iminohydantoins by starting with the corresponding (+)- or (-)-amino acids. Compound **1** was also synthesized by a published procedure[18] by reacting benzil with guanidine, and its physicochemical and spectral data were compared with those of **1** prepared from the above procedure for verification purpose.

The reaction of benzil with 1-methylguanidine resulted in formation of two major crystalline products which were isolated by fractional crystallization. The spectral data for the less soluble product suggested it to be *N*-methyl-5,5-diphenyl-2-iminohydantoin (**11**), and this was confirmed by reacting methylamine with 2-(methylthio)-4,4-diphenyl-5-imidazolinone to give product with identical physicochemical and spectral properties as **11**. The more soluble product was assigned as 3-methyl-5,5-diphenyl-2-iminohydantoin (**12**), and its structure was confirmed by comparing its physicochemical data, spectral data with those of the same product reported,[22] which was prepared by the reaction of **1** with methyl iodide.

Results and Discussion

The iminohydantoin analogue of phenytoin, viz., **1**, and its immediate chemical precursor **6** were initially tested against MES and scMET tests in mice by the Epilepsy Branch, Division of Convulsive, Developmental, and Neuromuscular Disorders, NIH, Bethesda, MD. To our surprise, both of these compounds failed to produce any significant anticonvulsant activity up to a dose of 300 mg/kg. The tests were repeated in our laboratory and the same negative finding was observed up to a dose of 3000 mg/kg. It was difficult to rationalize these findings in view of such a close structural resemblance of **1** to phenytoin and thiophenytoin. It has been reported[23] that 2-thio-

(21) Kwon, C.-H.; Nagasawa, H. T.; DeMaster, E. G.; Shirota, F. N. *J. Med. Chem.* **1986**, *29*, 1922.
(22) Lempert, K.; Breuer, J. *Chem. Ber.* **1959**, *92*, 1710.
(23) Kutt, K. V. H.; Sohn, Y. J.; Levitt, B.; Raines, A. *Eur. J. Pharmacol.* **1970**, *10*, 106.
(24) Goehring, R. R.; Greenwood, T. D.; Nwokogu, G. C.; Pisipati, J. S.; Rogers, T. G.; Wolfe, J. F. *J. Med. Chem.* **1990**, *33*, 926.

Table I. Preliminary Anticonvulsant Testing Data I[a]

compound	optical config	scMET[b] 0.5 h	scMET[b] 4 h	mES[c] 0.5 h	mES[c] 4 h
1		–	–	–	–
6		–	–	–	–
7		–	–	–	–
3a	*S*	+	–	++	–
3b	*R*	+	–	ND[d]	–
8a	*S*	+++	–	++	++
8b	*R*	+	–	–	–
4a	*S*	–	ND	ND	ND
9a	*S*	+++	+++	+++	+++
9b	*R*	++	+	ND	ND
5		–	–	–	–
10		+	++	–	–
11		–	–	–	–
12		–	–	–	–

[a] Drugs were delivered intraperitoneally. +++, ++, and + denote activity at 30, 100, and 300 mg/kg, respectively. [b] Subcutaneous Metrazol seizure test. [c] Minimal electroshock seizure test. [d] ND = not determined.

Table II. Anticonvulsant Testing Data II

compound	ED_{50}[a] scMET[b]	ED_{50}[a] mES[c]
3a	>1000	97.8 (33.0–289)[d]
8a	>1000	213 (71.9–632)
4a	>300 and <1000	ND
9a	92.8 (48.5–178)	44.5 (18.1–108)
9b	547 (153–1959)	ND
10	NA	459 (67.1–3144)
thiophenytoin	1335 (675–2644)	NA
phenytoin	NA	2.3 (0.90–5.9)

[a] ED_{50} values are in milligrams/kilogram of test drug delivered intraperitoneally and measured at 0.5 h. ND = not determined. NA = not active. [b] Subcutaneous Metrazol seizure test. [c] Minimal electroshock seizure test. [d] Numbers in parentheses are 95% confidence intervals.

phenytoin is considerably more lipophilic than phenytoin, and our comparative TLC analysis of 2-thiophenytoin, phenytoin, and **1** indicated that **1** was the least nonpolar compound, followed by phenytoin, and 2-thiophenytoin [R_f = 0.38, 0.69, and 0.97 in CH_3OH–CH_2Cl_2 (1:9), respectively]. The steric size and conformational structure of **1** should be essentially the same as phenytoin; therefore it was conceivable that lack of activity of **1** was perhaps due to its unfavorable pharmacokinetic properties, e.g., incomplete absorption and/or incomplete penetration across the blood–brain barrier. *N*-Methyl-substituted diphenyliminohydantoins, viz., **11** and **12**, were synthesized to enhance lipophilicity with minimal change in steric size and to examine the ability to form hydrogen bonds in the anticonvulsant activity. Both of these compounds were ineffective against scMET/MES tests but showed observable but weak activities against mES test (ED_{50} > 500 mg/kg).

We then proceeded to examine the substituent effect at C-5 on the iminohydantoin ring (Tables I and II). The mono-phenyl-substituted compound **2** could not be synthesized for testing; however its carbobenzoxy derivative **7** was tested and shown to be devoid of any significant activity. Initial studies on the 5-benzyl-substituted iminohydantoins showed that the *S* isomers **3a** and **8a** were active against mES test as well as scMET test; however the subsequent quantitative testings did not provide good dose–response characteristics against scMET test. Additionally, the *R* isomers **3b** and **8b** failed to show any significant anticonvulsant activity. Studies on the 5-isobutyl-substituted iminohydantoins showed the similar pattern of differences in activity by the stereoisomers. The 1-carbobenzoxy-substituted *S* isomer **9a** was active against both mES and scMET tests. On the other hand, its *R* isomer **9b** was considerably less active than **9a**. The unprotected *S* isomer **4a** was also less active than **9a**. The unsubstituted iminohydantoin **5** failed to show any activity, but the 1-carbobenzoxy derivative **10** showed a weak activity against mES test. It was apparent from this study that the 1-carbobenzoxy-substituted iminohydantoins generally showed higher activities than the corresponding counterparts. It is however not known whether the intact carbobenzoxy moiety is an important structural feature for activity or is only contributing toward the enhanced lipophilicity. The carbobenzoxy group may readily by hydrolyzed by the action of ubiquitous amidases/esterases and therefore may simply serve as a bioreversible lipophilic promoiety of the iminohydantoins. On the other hand, the intact carbobenzoxy moiety may be an important integral component of the 2-iminohydantoins. This moiety not only adds an increased hydrophobic and steric factors to the molecules but also may influence other factors, e.g., pK_a and the ability to undergo tautomeric exchanges between the endo- and exo-cyclic imines, which may also play important roles in providing enhanced anticonvulsant activity.

Among the iminohydantoins screened, the anticonvulsant activity of the most active member **9a** was also confirmed by the Epilepsy Branch, NIH. The anticonvulsant activity of **9a** and its protective index (PI) was compared with some of the structurally related, ureide-containing anticonvulsant drugs (Table III). The data show that **9a** is approximately 10-fold less potent than phenytoin against MES test, but the former is also active against scMET test, suggesting its wider clinical potential. The Phase II anticonvulsant activity profile of **9a** appears to closely match that of phenacemide, an open-chain ureide structure.

In summary, the pharmacological data obtained in this investigation suggest that the SAR of 2-iminohydantoins is quite different from that of hydantoin series in view of the lack of any significant activity by **1**. The notable anticonvulsant activity of **9a** against MES/mES and scMET tests suggests that the SAR of 2-iminohydantoins

Table III. Summary of Phase II Evaluation of **9a** in Comparison with Prototype Drugs

compound	ED_{50}[a] MES	ED_{50}[a] scMET	tox, TD_{50}	PI[b] MES	PI[b] scMET
9a	98.6 (67.0–141.4)[c]	140.7 (88.7–214.4)	349.5 (252.9–400)	3.5	2.5
phenytoin[d]	9.5	NA[f]	65.5	6.9	
mephenytoin[e]	61	31	154	2.5	5.0
phenacemide[e]	87	116	421	4.8	3.6
phenobarbital[d]	21.8	13.2	69.0	3.2	5.2
ethosuximide[d]	>1000	130.4	440.8		3.4

[a] ED_{50} and TD_{50} (rotorod ataxia test; neurotoxicity) values are in milligrams/kilogram of test drug delivered intraperitoneally and measured at time of peak effect or peak neurologic deficit. [b] PI = protective index (TD_{50}/ED_{50}). [c] Numbers in parentheses are 95% confidence intervals. [d] Reference 24. [e] Reference 6. [f] NA = not active.

may be similar to that of 2-thiohydantoins. Research is in progress to examine this hypothesis and to further define the SAR of 2-iminohydantoins.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and were uncorrected. Microanalyses were performed by Atlantic Microlab, Inc., Norcross, GA. The following instruments were used: IR, Perkin-Elmer Model 281; ^{1}H NMR, Varian EM-360L CW, 60 MHz (Me_4Si as internal standard); Polarimeter, Perkin-Elmer Model 241. Silica gel GF plates (250 μ, Analtech) were used for thin-layer chromatography (TLC). All chemicals and solvents were reagent grade and were purchased from commercial vendors. 5,5-Diphenylhydantoin and 5,5-diphenyl-2-thiohydantoin were purchased from Aldrich and used without further purification.

***N*-Carbobenzoxy-2,2-diphenylglycine.** Benzyloxycarbonyl chloride (3.41 g, 2.86 mL, 0.02 mol) in 15 mL of THF was added to a suspension of 2,2-diphenylglycine (4.55 g, 0.02 mol) and NaOH (0.84 g, 0.02 mol) in THF/H_2O (50 mL/50 mL) at ice bath temperature. The reaction was allowed to proceed for 3 h at this temperature, then another equivalent of each of benzyloxycarbonyl chloride and NaOH was added, and the reaction mixture was stirred at room temperature overnight. The mixture was concentrated to half of its volume in vacuo. The resulting aqueous solution (pH 9.4) was further basified to pH 12 by 10% NaOH and extracted with methylene chloride (3 × 50 mL). The aqueous layer was separated, acidified to pH 2.5, and extracted with EtOAc (3 × 50 mL). The separated organic layer was dried over anhydrous sodium sulfate and the filtrate was evaporated in vacuo to give 7.0 g of the crude product as thick yellow liquid. This was used to synthesize **6** without further purification: ^{1}H NMR ($CDCl_3$) δ 7.53–7.12 (fused d, 15 H, ArH), 4.90 (2, 2 H, CH_2O).

1-Carbobenzoxy-5,5-diphenyl-2-iminohydantoin (6). A mixture of *N*-carbobenzoxy-2,2-diphenylglycine (14.75 g, 0.04 mol), DCC (8.25 g, 0.04 mol), and *N*-hydroxysuccinimide (4.60 g, 0.04 mol) was stirred in 100 mL of THF at ice bath temperature for 3 h. The reaction mixture was filtered and the filtrate was added dropwise to a solution of monosodium cyanamide (7.68 g, 0.12 mol) in 100 mL of H_2O at ice bath temperature. After stirring overnight at room temperature, the mixture was concentrated in vacuo to remove THF and filtered. The aqueous filtrate (pH 10.4) was further basified to pH 12 with 10% NaOH and extracted with methylene chloride (3 × 50 mL). The methylene chloride extract contained essentially all of the UV quenching materials and it was evaporated in vacuo to give crude *N*-carbobenzoxy-2,2-diphenylglycylcyanamide sodium salt as thick yellowish liquid: IR (Nujol, cm^{-1}) 3400 (NH), 2140 (N=C=N$^-$), 1700 (C=O), 1640 (C=N). Addition of H_2O to this liquid in an attempt to remove water soluble byproducts resulted in formation of a solid product (10.13 g). This solid was filtered and crystallized from hot methanol to give 9.16 g (59.4% yield) of **6**: mp 187–188 °C; TLC R_f = 0.73 in MeOH/CH_2Cl_2 (1:9); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 7.01–7.41 (m, 15 H, ArH), 4.96 (s, 2 H, OCH_2), 3.49 (br, 1 H, NH); IR (Nujol, cm^{-1}) 3400, 3300 (NH), 1700 (C=O), 1650 (C=N). Anal. ($C_{23}H_{19}N_3O_3$) C, N; H: calcd, 4.96; found, 5.45.

5,5-Diphenyl-2-iminohydantoin (1). Method A. Compound **6** (3.0 g, 7.8 mmol) was subjected to catalytic transfer hydrogenation with 9% palladium on charcoal (1.0 g) and ammonium formate (2.3 g) in 200 mL of methanol at room temperature for 1 h. The reaction mixture was filtered through a bed of Celite and the filtrate was evaporated in vacuo to give 0.6 g of a crude solid product. This was crystallized from methanol to give 0.4 g (20% yield) of **1**: mp 354–355 °C; TLC R_f = 0.38 in MeOH/CH_2Cl_2 (1:9); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 6.91–7.45 (m, 10 H, ArH), 3.24 (br, 1 H, NH); IR (Nujol, cm^{-1}) 3400 (NH), 1700 (C=O), 1650 (C=N). Anal. ($C_{15}H_{13}N_3O$) C, H, N.

Method B. A mixture of benzil (2.10 g, 0.010 mol), guanidine carbonate (1.35 g, 0.015 mol), and KOH (1.12 g, 0.020 mol) in 50 mL of ethanol was refluxed for 3.5 h. After cooling, ethanol was removed in vacuo and the resulting solid was crystallized from hot methanol to give 1.68 g (80% yield) of **1**: mp 354–356 °C (lit.[18] mp 290 °C); TLC R_f = 0.37 in MeOH/CH_2Cl_2 (1:9); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 6.92–7.45 (m, 10 H, ArH), 3.24 (br, 1 H, NH); IR (Nujol, cm^{-1}) 3400 (NH), 1700 (C=O), 1650 (C=N).

Preparation of *N*-Methyl-5,5-diphenyl-2-iminohydantoin (11) and 3-Methyl-5,5-diphenyl-2-iminohydantoin (12) from Benzil and 1-Methylguanidine. A mixture of 1-methylguanidine hydrochloride (2.19 g, 0.02 mol) and benzil (4.20 g, 0.02 mol) in 40 mL of ethanol and KOH (1.68 g, 0.03 mol) in 3 mL of H_2O was refluxed for 3.5 h. After cooling, the mixture was evaporated in vacuo to near dryness. The resulting semisolid residue was mixed with H_2O (25 mL) and methylene chloride (25 mL) whereupon white precipitate was formed between the aqueous and organic layer. The precipitate was filtered and crystallized from hot methanol to give 1.33 g of **11**: mp 324–326 °C; TLC R_f = 0.43 in MeOH/CH_2Cl_2 (1:9); ^{1}H NMR (DMSO-d_6) δ 7.30 (s, 10 H, ArH), 2.61 (s, 3 H, NCH_3). Anal. ($C_{16}H_{15}N_3O$) C, H, N.

The above filtered methylene chloride portion was dried over anhydrous sodium sulfate, the filtrate was evaporated in vacuo, and the resulting solid residue was crystallized from methylene chloride to give 0.55 g of **12**: mp 238–239 °C (lit.[22] mp 238–239 °C); TLC R_f = 0.59 in MeOH/CH_2Cl_2 (1:9); ^{1}H NMR ($CDCl_3$) δ 7.00–7.50 (m, 10 H, ArH), 3.00 (NCH_3); IR (Nujol, cm^{-1}) 3400 (NH), 1710 (C=O), 1650 (C=N). Anal. ($C_{16}H_{15}N_3O \cdot {}^1/_2H_2O$) C, H, N.

Preparation of *N*-Methyl-5,5-diphenyl-2-iminohydantoin (11) from 2-(Methylthio)-4,4-diphenyl-5-imidazolinone and Methylamine. A solution of 2-(methylthio)-4,4-diphenyl-5-imidazolinone (2.82 g, 0.01 mol) and methylamine (0.68 mL, 0.02 mol) in 10 mL of ethanol contained in a sealed tube was heated on a steam bath for 2 h. After cooling to room temperature, the resulting precipitate was filtered to give 2.00 g of crystalline crude product. This was recrystallized from hot ethanol to give 1.46 g (55% yield) of **11**: mp 326–328 °C (lit.[22] mp 322–324 °C); TLC R_f = 0.43 in MeOH/CH_2Cl_2 (1:9); ^{1}H NMR (DMSO-d_6) δ 7.30 (s, 10 H, ArH), 2.61 (s, 3 H, NCH_3).

2-(Methylthio)-4,4-diphenyl-5-imidazolinone. A mixture of 5,5-diphenyl-2-thiohydantoin (4.8 g, 0.018 mol) dissolved in 5 mL of MeOH, NaOH (0.78 g, 0.02 mol) dissolved in 5 mL of H_2O, and iodomethane (1.25 mL, 0.02 mol) in a sealed tube was heated on a steam bath for 2 h. After cooling to room temperature, the resulting crystalline precipitate was filtered to give 3.65 g (71.8% yield) of the desired product: mp 202–204 °C; TLC R_f = 0.70 in EtOAc/hexane (5:4); ^{1}H NMR ($CDCl_3$) δ 7.60 (s, 10 H, ArH), 2.90 (SCH_3).

(±)-*N*-Carbobenzoxy-2-phenylglycine. Benzyl carbonochloridate (3.41 g, 2.86 mL, 0.02 mol) in 15 mL of THF and 10% aqueous NaOH (0.84 g, 8.0 mL, 0.02 mol) were added dropwise via separate channels to a suspension of (±)-2-phenylglycine (3.02 g, 0.02 mol) and NaOH (0.84 g, 0.02 mol) in THF/H_2O (50 mL/50 mL) at ice bath temperature. After stirring overnight at room temperature, the mixture was concentrated to half of its volume in vacuo. The resulting aqueous solution (pH 9.4) was further basified to pH 12 by 10% NaOH and extracted with methylene chloride (3 × 50 mL). The aqueous layer was separated, acidified to pH 2.2, and extracted with EtOAc (3 × 50 mL). The separated organic layer was dried over anhydrous sodium sulfate and the filtrate was evaporated in vacuo to give 4.79 g of the crude product as white solid: R_f = 0.73 EtOAc/AcOH (100:1). This was used to synthesize **7** without further purification: ^{1}H NMR ($CDCl_3$) δ 10.30 (s, 1 H, COOH), 6.82–7.45 (m, 10 H, ArH), 5.18 (s, 1 H, CH), 5.03 (s, 2 H, CH_2O).

(±)-1-Carbobenzoxy-5-phenyl-2-iminohydantoin (7). A mixture of (±)-*N*-carbobenzoxy-2-phenylglycine (2.85 g, 0.01 mol), DCC (2.06 g, 0.01 mol), and *N*-hydroxysuccinimide (1.15 g, 0.01 mol) was stirred in 100 mL of THF at ice bath temperature for 3 h. The reaction mixture was filtered and the filtrate was added dropwise to a solution of monosodium cyanamide (1.92 g, 0.03 mol) in 100 mL of H_2O at ice bath temperature. After stirring overnight at room temperature, the mixture was concentrated in vacuo to remove THF and filtered. The aqueous filtrate (pH 10.4) was further basified to pH 12 with 10% NaOH and extracted with methylene chloride (3 × 50 mL). The aqueous layer was separated, acidified to pH 2.2, and extracted with EtOAc (3 × 50 mL). The EtOAc extract was evaporated after drying over anhydrous sodium sulfate in vacuo to give a thick yellow liquid: IR (Nujol, cm^{-1}) 3400 (NH), 2260 (—NHC≡N), 1710 (C=O), 1640 (C=N). Addition of H_2O to this liquid resulted in formation of a solid product. This solid was crystallized from hot methanol to give 2.60 g (70.6% yield) of **7**: mp 225–226 °C; TLC R_f = 0.63 in MeOH/CH_2Cl_2 (1:9); IR (Nujol, cm^{-1}) 3500, 3380 (NH), 3040 (C_6H_5), 1740, 1700 (C=O),

1660 (C=N); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 6.58–7.32 (m, 10 H, ArH), 5.17 (s, 1 H, CH), 5.00 (s, 2 H, OCH_2), 3.33 (br, 1 H, NH). Anal. ($C_{17}H_{15}N_3O_3$) C, H, N.

(*S*)-(+)-1-Carbobenzoxy-5-benzyl-2-iminohydantoin (8a) was prepared with use of (+)-*N*-carbobenzoxyphenylalanine on a 0.02-mol scale in the procedure for **7** to give crude *N*-carbobenzoxy-L-phenylalanylcyanamide as a thick yellow liquid. This liquid was diluted in a small amount of ethanol and heated in the steam bath for 5 min. Addition of H_2O to this resulted in formation of a solid product. This solid was crystallized from EtOAc/hexane to give 4.10 g (63.4% yield) of **8a**: mp 173–175 °C; $[\alpha]^{23}_D$ +120.2 (*c* = 1.0, MeOH); TLC R_f = 0.55 in MeOH/CH_2Cl_2 (1:9); IR (Nujol, cm^{-1}) 3400 (NH), 3040 (C_6H_5), 1740, 1700 (C=O), 1650 (C=N); ^{1}H NMR ($CDCl_3$) δ 6.65–7.69 (m, 10 H, ArH), 5.30 (s, 2 H, OCH_2), 4.25–4.49 (t, 1 H, CH), 3.11–3.29 (d, 2 H, CH_2). Anal. ($C_{18}H_{17}N_3O_3$) C, H, N.

(*R*)-(−)-1-Carbobenzoxy-5-benzyl-2-iminohydantoin (8b) was prepared with use of (−)-*N*-carbobenzoxyphenylalanine on a 0.02-mol scale in the procedure for **8a** to give crystalline **8b** in 62% yield: $[\alpha]^{23}_D$ −121.4 (*c* = 1.0, MeOH).

(*S*)-(−)-5-Benzyl-2-iminohydantoin (3a). Compound **8a** (1.00 g, 3.09 mmol) was subjected to catalytic transfer hydrogenation with 9% palladium on charcoal (0.34 g) and ammonium formate (0.77 g) in 50 mL of methanol for 2 h. The reaction mixture was filtered through a bed of Celite and the filtrate was evaporated in vacuo to give 0.45 g of a crude solid product. The solid was washed with water and crystallized from ethanol to give 0.30 g (51% yield) of **3a**: mp 255–258 °C; $[\alpha]^{23}_D$ −134.7 (*c* = 1.0, MeOH); TLC R_f = 0.32 in MeOH/CH_2Cl_2 (1:9); IR (Nujol, cm^{-1}) 3350 (NH), 3040 (C_6H_5), 1700 (C=O), 1650 (C=N); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 6.79–7.71 (m, 5 H, ArH), 3.75–4.25 (t, 1 H, CH), 2.75–3.08 (d, 2 H, CH_2). Anal. ($C_{10}H_{11}N_3O$) C, H, N.

(*R*)-(+)-5-Benzyl-2-iminohydantoin (3b) was prepared from **8b** on a 3.09-mmol scale in the procedure for **3a** to give 0.28 g (47.7% yield) of **3b**: $[\alpha]^{23}_D$ +134.65 (*c* = 1.0, MeOH).

(*S*)-(+)-1-Carbobenzoxy-5-isobutyl-2-iminohydantoin (9a) was prepared with use of (−)-*N*-carbobenzoxyleucine on a 0.02-mol scale in the procedure for **7** to give a thick yellow liquid. This liquid was heated in a steam bath to give a solid product and the solid was crystallized from CH_2Cl_2/hexane to give 4.71 g (81.4% yield) of **9a**: mp 170–173 °C (lit.[20] mp 169–171 °C); $[\alpha]^{23}_D$ +22.68 (*c* = 1.0, MeOH); TLC R_f = 0.68 in MeOH/CH_2Cl_2 (1:9); IR (Nujol, cm^{-1}) 3400, 3140 (NH), 3040 (C_6H_5), 1750, 1710 (C=O), 1660 (C=N); ^{1}H NMR ($CDCl_3$) δ 7.90 (br, 1 H, NH), 7.21–7.59 (m, 5 H, ArH), 5.30 (s, 2 H, OCH_2), 4.09–4.35 (fused t, 1 H, CH), 1.51–2.08 (m, 3 H, CH and CH_2), 0.59–0.98 (m, 6 H, CH_3). Anal. ($C_{15}H_{19}N_3O_3$) C, H, N.

(*R*)-(−)-1-Carbobenzoxy-5-isobutyl-2-iminohydantoin (9b) was prepared with use of (+)-*N*-carbobenzoxyleucine on a 0.02-mol scale in the procedure for **9a** to give 5.00 g (86.4% yield) of **9b**: $[\alpha]^{23}_D$ −21.0 (*c* = 1.0, MeOH).

(*S*)-(−)-5-Isobutyl-2-iminohydantoin (4a). Compound **9a** (1.50 g, 5.18 mol) was hydrogenated with 9% palladium on charcoal (1.50 g) in 50 mL of methanol for 1 h. The reaction mixture was filtered through a bed of Celite and the filtrate was evaporated in vacuo to give 0.51 g of a crude solid product. This solid was crystallized from EtOAc/hexane to give 0.40 g (50% yield) of **4a**: mp 234–237 °C; $[\alpha]^{23}_D$ −10.0 (*c* = 1.0, MeOH); TLC R_f = 0.279 in MeOH/CH_2Cl_2 (1:9); IR (Nujol, cm^{-1}) 3390, 3260 (NH), 1700 (C=O), 1650 (C=N); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 7.20 (br, 1 H, NH), 3.51–3.89 (fused t, 1 H, CH), 1.09–1.75 (m, 3 H, CH and CH_2), 0.29–0.85 (m, 6 H, CH_3). Anal. ($C_7H_{13}N_3O\cdot0.2H_2O$) C, H, N.

1-Carbobenzoxy-2-iminohydantoin (10) was prepared with use of *N*-carbobenzoxyglycine on a 0.02-mol scale in the procedure for **7** to give the crude product as white solid. This solid was crystallized from THF/hexane to give 2.94 g (63.0% yield) of **10**: mp 204–206 °C; TLC R_f = 0.55 in MeOH/CH_2Cl_2 (1:9); IR (Nujol, cm^{-1}) 3380, 3280 (NH), 1750, 1700 (C=O), 1640 (C=N); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 7.50 (s, 5 H, ArH), 5.25 (s, 2 H, OCH_2), 4.12 (s, 2 H, CH_2), 3.38 (br, 1 H, NH). Anal. ($C_{11}H_{11}N_3O_3$) C, H, N.

2-Iminohydantoin (5). Compound **10** (1.00 g, 4.28 mmol) was hydrogenated with 9% palladium on charcoal (1.00 g) in 50 mL of methanol for 1 h. The reaction mixture was filtered through a bed of Celite and the filtrate was evaporated in vacuo to give 0.30 g of the crude solid product. This was crystallized from ethanol to give 0.29 g (52.1% yield) of **5**: mp 275 °C dec; IR (Nujol, cm^{-1}) 3380 (NH), 1700 (C=O), 1640 (C=N); ^{1}H NMR [$CDCl_3$/DMSO-d_6 (1:7)] δ 3.62 (s, 2 H, CH_2), 3.28 (br, 1 H, NH). Anal. ($C_3H_5N_3O$) C, H, N.

Pharmacology. Adult, male Swiss-Webster mice (20–25 g, Taconic Farms, Germantown, NY) were used. The mice were housed in an environmentally controlled room (12 h light/dark cycle, lights on 07:00; 35–45% humidity; 20–23 °C) with food and water available ad libitum, except when removed from cages for testing. Drugs used for antiepileptic testing were dissolved in normal saline or suspended in 2% carboxymethylcellulose (CMC). All test drugs were injected intraperitoneally in a volume not exceeding 4.0 mL/kg. Dose–response characteristics were determined from at least three groups of mice (typically 6–8 mice/group) for each drug tested.

The drugs were screened against (1) chemically induced seizures utilizing pentylenetetrazole (80–85 mg/kg, sc) as the convulsant and (2) electrically induced seizures (minimal and supramaximal seizures; Electroshock Unit Model 11A, IITC, Landing, NJ) at 0.5 and 4.0 h after drug administration. Minimal electroshock seizures (mES) were induced by an 18 mAmp current (duration 0.2 s) delivered via corneal electrodes, whereas supramaximal electroshock seizures (MES, maximal electroshock) were elicited at a 50-mAmp current. Minimal electroshock seizures are induced by the minimum (threshold) current required to cause clonic convulsions in 100% of the test mice. The supramaximal electroshock test utilizes a current roughly 2–5 times greater than threshold in order to induce tonic hindlimb extension in 100% of the mice tested.

Compounds **1**, **6**, and **9a** were also screened by the Epilepsy Branch of NINCDS by using established protocols. Among these, **9a** advanced to Phase II.

Acknowledgment. We thank Mr. James Stables for providing pharmacological data through the Antiepileptic Drug Development Program, National Institutes of Health. We are also grateful to Professor Herbert T. Nagasawa at the University of Minnesota for initially suggesting this project.