Synthesis of Aminomethyl-Substituted Cyclic Imide Derivatives for Evaluation as Anticonvulsants[1]

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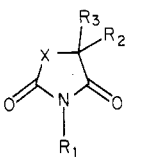
A series of aminomethyl-substituted cyclic imides (II) based on the 2,5-pyrrolidinedione (X = CH_2, succinimide) and 2,4-imidazolidinedione (X = NH, hydantoin) ring systems have been prepared. The compounds were designed on the basis of a potential interaction in the γ-aminobutyric acid (GABA) neurotransmitter system and evaluated for anticonvulsant activity. The 3-(aminomethyl)-2,5-pyrrolidinediones were prepared by a dehydration procedure beginning with *N*-benzyl-2-(aminomethyl)succinic acid, whereas the 3-(aminomethyl)-3-methyl-2,3-pyrrolidinediones were best obtained by fusion of the amine salts of 2-(aminomethyl)-2-methylsuccinic acid. The hydantoin derivative, 5-(aminomethyl)-5-methyl-2,4-imidazolidinedione, was obtained by standard procedures. Although none of the compounds tested showed significant activity against convulsions induced by pentylenetetrazole (PTZ), some showed significant activity against maximal electroshock seizures in mice. Possible reasons for the lack of anti-PTZ activity and directions for further testing are discussed.

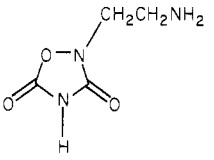
In recent years it has become increasingly evident that the functional status of the γ-aminobutyric acid (GABA) neurotransmitter system is important in convulsive states in mammalian species.[3] Antagonism of this neuronal system leads to convulsions, whereas facilitation provides protection from convulsant procedures. Furthermore, many therapeutically useful antiepileptic agents are now felt to exert at least part of their effects by facilitation of GABA neurotransmission. For example, the benzodiazepines are thought to produce most of their central effects by interaction with a receptor coupled to the GABA recognition site.[4] In addition, evidence is accumulating that depressant barbiturates also allosterically enhance GABA activity at yet another site that is probably on the associated chloride ionophore.[5] There is also evidence, although less substantial, that phenytoin exhibits an action on the GABA system similar to the barbiturates.[6] A site of action has not yet been identified for the oxazolidinediones or the succinimides, although a similar site of action to the barbiturates might be expected.[7]

With the exception of the benzodiazepines, all of the above antiepileptic drug classes possess bioisosteric heterocyclic ring systems, as seen in general structure I. A common feature of these ring systems is the weakly acidic imide moiety, which could conceivably function as a carboxyl equivalent. This supposition seems to be supported by the observation that quisqualamine (1), which also



I

class	X
barbiturate	CONH
hydantoin	NH
oxazolidinedione	O
succinimide	CH_2



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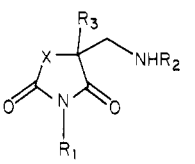

II

contains an imide moiety, elicits an action on spinal neurons qualitatively resembling the effects of pentobarbital.[8] Thus, even though apparently not interacting at the GABA recognition site, if one considers the imide moiety as a carboxyl bioisostere, quisqualamine can be seen to possess the equivalent of the GABA molecule within its framework.

From available evidence, it cannot yet be concluded with certainty that all of these imide-type anticonvulsant agents interact at the same receptor site. Nevertheless, for some reason a common structural requirement for anticonvulsant activity in these classes of compounds seems to be the presence of the weakly acidic imide moiety or its metabolic precursor.

The presence of a basic group in the side chain of these heterocyclic imides may also be of value. In addition to quisqualamine, the incorporation of a *p*-amino group into such drugs as mephobarbital[9] and methsuximide[10] also produces compounds with useful anticonvulsant properties.

Based on considerations such as those discussed above, it seemed desirable to examine the effect of incorporation of an appropriately positioned primary amine function into the side chains of these commonly employed antiepileptic

(1) (a) Preliminary reports of portions of this work were presented in May, 1981, at the Central and Great Lakes Joint Regional American Chemical Society Meeting, Dayton, OH, and in June, 1982, at the Great Lakes Regional American Chemical Society Meeting, Normal, IL. (b) Taken in part from the Ph.D. Dissertation submitted to the Graduate School of West Virginia University by R.W.C., Jr., Aug 1982.
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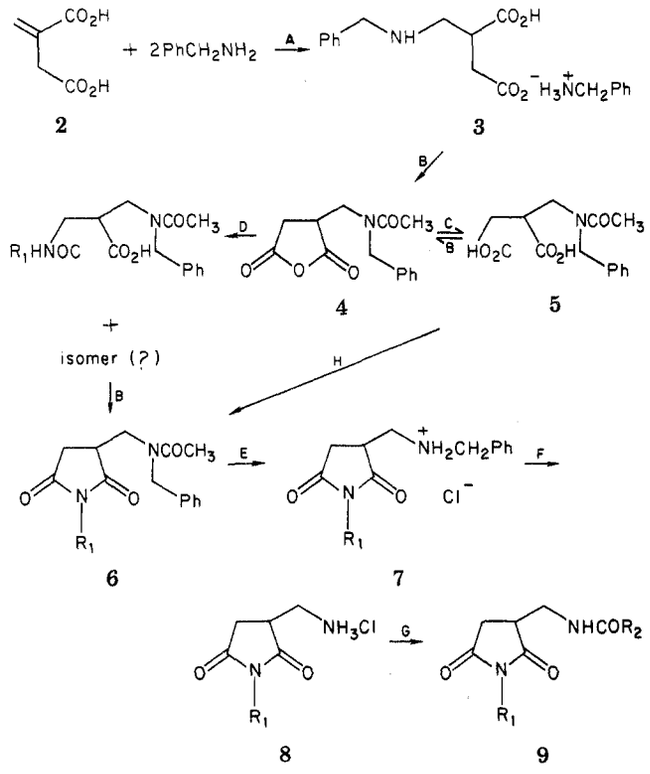
Scheme I[a]

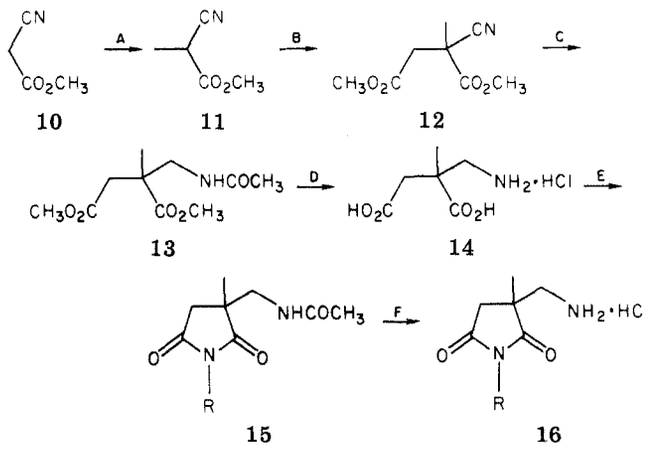


[a] Reaction conditions: A = H_2O; B = Ac_2O; C = H_2O; D = R_1NH_2, CH_2Cl_2, or R_1NH_3Cl, TEA, THF; E = 6 N HCl; F = H_2, 10% Pd/C; G = R_2COCl, TEA, THF; H = NH_3/MeOH then fuse.

agents. Therefore, compounds of the type indicated by general structure II were prepared for evaluation as anticonvulsants.

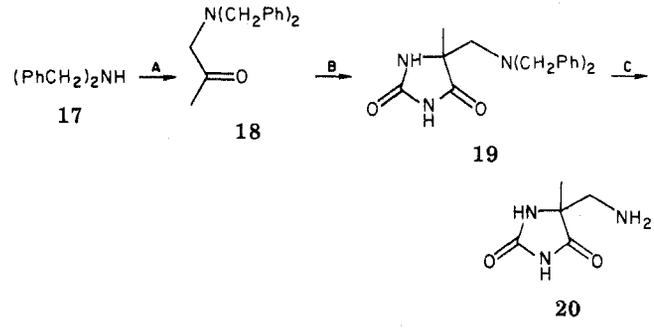
Chemistry. The compounds of general structure II selected for initial investigation were succinimides (X = CH_2) where R_3 = H. Preparation of the desired compounds was accomplished according to the reaction sequence shown in Scheme I. The 1,4-adduct **3** was prepared from itaconic acid (**2**) and benzylamine as described by Zilkha and co-workers.[11] Interestingly, attempted isolation of the conjugate addition products of **2** and various other amines, under a variety of conditions, was completely unsuccessful. This apparent adduct instability may be related to our inability to isolate the free amino diacid of **3** in acceptable yield as was reported by Zilkha and co-workers.[11] As a result of this difficulty, adduct **3** was treated with acetic anhydride to produce anhydride **4** (along with benzylacetamide), from which diacid **5** was isolated after mild aqueous hydrolysis as a clear, colorless glass. Redehydration of **5**, followed by treatment with benzyl- or methylamine, presumably produced a mixture of isomeric acid diamides, which were not isolated but directly treated with acetic anhydride to give imides **6**. Acid-catalyzed hydrolysis gave crystalline secondary amines **7**, from which the corresponding primary amines **8** were obtained by hydrogenolysis. Amide derivatives **9** were prepared by standard procedures employing the desired acyl chloride. Attempts to prepare the imide unsubstituted system (**6**, R_1 = H) by analogous procedures were unsuccessful, producing instead a complex mixture of products. However, this compound was isolated from the product mixture resulting from fusion of the ammonium salt of **5** in 66% yield.

Scheme II[a]



[a] Reaction conditions: A = $(CH_2O)_n$, piperidine acetate, 5% Pd/C, H_2; B = $BrCH_2CO_2Et$, NaOMe, MeOH; C = H_2, Ra-Ni, Ac_2O, NaOAc; D = 1 N HCl; E = Ac_2O, NaOH, H_2O, RNH_2, then fuse at 185 °C; F = 1 N HCl.

Scheme III[a]



[a] Reaction conditions: A = $ClCH_2COCH_3$, TEA, THF; B = $(NH_4)_2CO_3$, KCN, H_2O, EtOH; C = H_2, 10% Pd/C, EtOH.

The route employed for the methyl-substituted succinimides is outlined in Scheme II. Reductive methylation of methyl cyanoacetate (**10**) produced crude propionate derivative **11** (which was not further purified due to extensive decomposition on attempted distillation). Treatment of crude **11** with sodium methoxide in methanol, followed by ethyl bromoacetate, provided nitrile diester **12**. Several methods of reduction of nitrile **12** were investigated without success; however, amide **13** was eventually obtained in 89% yield upon hydrogenation over Raney nickel W-2 in acetic anhydride–sodium acetate. Acid-catalyzed hydrolysis then afforded the common intermediate **14** in good yield. Although attempts to prepared **15** by the acetic anhydride dehydration procedure described above produced complex mixtures, preparation of the acetamide of **14** and then fusion of the appropriate amine salt in a sealed pressure bottle under a nitrogen atmosphere afforded good yields of amides **15**. The desired primary amines were then obtained by acid-catalyzed hydrolysis.

Synthesis of the hydantoin system (II, X = NH, R_3 = CH_3) was accomplished according to the sequence in Scheme III. Reaction of dibenzylamine (**17**) with chloroacetone in the presence of triethylamine afforded ketone **18** in good yield. Under the conditions of the Bucherer–Bergs reaction,[12] **18** was converted to hydantoin **19**, which was smoothly debenzylated to afford crystalline **20**.

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Table I. Results of Phase I Anticonvulsant Testing of Compounds II[a]

compd	X	R_1	R_2	R_3	MES[b] 0.5 h	MES[b] 4 h	PTZ[c] 0.5 h	PTZ[c] 4 h	NT[d]
7a	CH_2	$PhCH_2$	$PhCH_2$	H	+++	−	−	−	−(4)
8a	CH_2	$PhCH_2$	H	H	+++	−	−	−	++ (4)
9c	CH_2	$PhCH_2$	CH_3CO	H	+	−	+	−	−(0)
15a	CH_2	$PhCH_2$	CH_3CO	CH_3	++	−	+	−	+(0)
16a	CH_2	$PhCH_2$	H	CH_3	+++	+	−	−	++ (2)

[a] +++, ++, and + denotes activity at 30, 100, 300 or 600 mg/kg, respectively; − denotes inactive at up to 600 mg/kg. [b] Anti maximal electroshock activity at 0.5 and 4 h after compound administration. [c] Anti-pentylenetetrazole activity at 0.5 and 4 h after administration. [d] Rotarod neurotoxicity; number in parentheses is number of deaths from respiratory depression among four animals given the 600 mg/kg dose of test compound.

Biological Results and Discussion

Preliminary pharmacological testing of the compounds submitted was performed in mice by the National Institute of Neurological and Communicative Disorders and Stroke Antiepileptic Drug Development Program. Although the design of these compounds was based on a hypothesized importance of an unsubstituted imide functionality, compounds substituted on the imide nitrogen were also submitted for testing. It was felt that the presence of the imide substituents might improve the transport properties of these compounds, which were anticipated to be very hydrophilic. Furthermore, *N*-methyl imides are readily N-demethylated in vivo, and such metabolites contribute, at least in part, to their anticonvulsant properties.[13] *N*-Benzylsuccinimides have also been shown to possess anticonvulsant activity, although their time of peak effect is significantly longer than for unsubstituted or *N*-methyl derivatives.[14] The results of phase I study in the Anticonvulsant Screening Project indicated that only those compounds possessing an imide *N*-benzyl substituent demonstrated any anticonvulsant activity in the models employed (Table I). Furthermore, significant activity was observed only against maximal electroshock induced seizures. Of the four compounds initially submitted for testing (**7** and **8**), that which most closely corresponds to the structural parameters employed in the design of this project (**8b**) was not only inactive but failed to show acute toxicity even at 600 mg/kg. This suggested the possibility that **8b** was not penetrating into the CNS to a sufficient extent, probably due principally to hydrophilicity, although chemical and/or metabolic lability could also play a role. For these reasons, *N*-acyl derivatives **9** and **15**, which mask the basic amine function, and methylated derivative **16**, which should be chemically and metabolically more stable, were prepared and submitted for testing. Neither modification, however, produced beneficial results in the test systems employed, and again, only compounds with the more lipophilic and less metabolically labile imide *N*-benzyl substituent[15] showed any real activity attributable to CNS effects. In fact, benzoylation of **8a** to give **9a** abolished the CNS activity seen for the parent compounds. Interestingly, acetylation of the primary amines **8a** and **16a** caused a lesser reduction in anti maximal electroshock activity, and these acetamides (**9c** and **15a**) showed the only observed activity, albeit weak, against seizures induced by pentylenetetrazole (PTZ).

The *N*-benzyl imides containing the basic side chain (**7a**, **8a**, and **16a**) were selected for phase II quantification of anti maximal electroshock activity and neurotoxicity by the Anticonvulsant Drug Development Program, and the results are shown in Table II. These compounds were found to be comparable to phensuximide and methsuximide in activity toward maximal electroshock-induced seizures and toxicity but significantly less active than standard drugs used in treatment of major convulsive seizures (e.g., phenytoin: ED_{50} = 9.50 mg/kg; TD_{50} = 65.5 mg/kg[16]).

Table II. Results of Phase II Quantification of Anti Maximal Electroshock Activity and Neurotoxicity

compd	MES ED_{50},[a] mg/kg	rot. TD_{50}, mg/kg
7a	136.5 (109.7-164.6)[b]	267.4 (245.0-292.0)[b]
8a	107.8 (94.5-123.0)	268.4 (245.1-284.9)
16a	66.4 (63.8-69.1)	227.6 (205.1-256.7)
phensuximide[c]	112 (104-131)	232 (187-267)
methsuximide[c]	76.3 (62.6-89.3)	188 (160-236)

[a] Measured at time of peak effect, 0.5 h. [b] Values in parentheses are 95% confidence intervals determined by probit analysis. [c] Values from ref 16.

Nominal support for the proposed distance separation between the basic side chain and imide moiety is seen by comparison with the previously reported one-carbon-shorter side-chain homologues.[17] The ED_{50} values obtained for our (aminomethyl)succinimides are 2 to 3 times lower than those for the corresponding aminosuccinimides.

The more significant compounds with respect to the features governing the design of these molecules were uniformly ineffective in the phase I studies, showing no effects, including toxicity, attributable to CNS activity. Since a likely reason for this might be the lack of penetration of the relevant compound into the CNS, it seemed of interest to determine if activity was present when the blood–brain barrier was circumvented. The effects of selected compounds were thus examined upon intracerebroventricular administration against PTZ-induced seizures. This convulsant was employed because available evidence suggests that pentylenetetrazole acts, at least in part, by some perturbation of GABA-mediated neurotransmission.[18] Compounds **8a,b**, **16c**, and **20** were administered in saline in 10 μL volumes into the lateral ventricle of the mouse brain according to the method of Haley and McCormick.[19] The mice were then injected intraperitoneally with an 85 mg/kg dose of PTZ 10 min later. No protection against PTZ-induced convulsions was

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noted at any of the doses employed (ranging from 0.1 to 10 μmol). However, when the *N*-benzyl-substituted **8a** was administered at 10 μmol, all of the five mice injected died of respiratory depression, and pronounced sedation was still seen at 1.0 μmol. On the other hand, when the free imide compounds **16c** and **20** were injected, four of the five mice died from tonic–clonic convulsions at the highest doses administered (10 and 1.0 μmol, respectively).

The lack of anti-PTZ activity for the compounds described in this work does not refute the original hypothesis in that there are several alternative explanations. It is possible, for example, that an aminoethyl side chain, as seen in quisqualamine (1), may be more desirable even though compounds of general structure II also possess the GABA skeleton. A report that the corresponding hydantoin derivative, 5-(aminoethyl)-2,4-imidazolidinedione, fails to bind to GABA receptors,[20] however, makes this unlikely.

The convulsant effects of compounds **16c** and **20** is also surprising in view of their close structural relationship to ethosuximide (I, X = CH_2; R_1 = H; R_2 = CH_3; R_3 = CH_2CH_3). It is well-known that minor structural changes in barbiturates may convert a depressant barbiturate into a convulsant.[21] Furthermore, both classes appear to interact at the same receptor sites in the GABA receptor complex.[5b,c,22] It seems possible, therefore, that the convulsant compounds prepared in this study may have produced a similar shift in profile. Receptor-binding experiments could possibly provide an explanation for the apparently anomolous behavior.

Experimental Section

All melting points (determined with a Thomas-Hoover capillary apparatus or Fisher-Johns hot stage) and boiling points are uncorrected. ^1H NMR spectra were recorded on a Varian Associates T-60 spectrometer with Me_4Si or 3-(trimethylsilyl)-1-propanesulfonic acid as internal standard. IR spectra were determined with a Perkin-Elmer 237B, a Beckman IR-18A, or a Perkin-Elmer 1310 infrared spectrophotometer. UV spectra were recorded in MeOH on a Cary 118 recording spectrophotometer. Electron-impact mass spectra were obtained with a Finnigan 4023 instrument at 70 eV. Catalytic hydrogenation was performed in a Parr pressure reaction apparatus. TLC was performed on silica gel 60 F_{254} precoated aluminum-backed plates from EM reagents. Unless otherwise noted, all column chromatography was performed on silica gel 60 (70–230 mesh) from EM reagents. Brine refers to a saturated solution of sodium chloride, while saturated $NaHCO_3$ refers to a saturated solution of sodium bicarbonate. Drying of organic extracts was performed by filtration through $MgSO_4$. Commercial nitrogen was dried by bubbling through concentrated H_2SO_4. Elemental analyses were performed either by Galbraith Laboratories, Knoxville, TN, or MicAnal, Tucson, AZ. Organic solvents were appropriately dried as necessary prior to use.

Benzylamine Salt of 2-[(Benzylamino)methyl]succinic Acid (3). This amino acid was prepared according to the method of Zilkha and co-workers.[11] A mixture of 45.0 g (0.35 mol) of itaconic acid and 74.9 g (0.7 mol) of benzylamine in 100 mL of H_2O was stirred at reflux for 1 h and then allowed to solidify by standing at 50 °C for 18 h. The resulting paste was vacuum filtered with acetone rinsing to afford 101.0 g (85%) of crude **3** as a light yellow cake. Recrystallization from 70% EtOH afforded 54.0 g (45%) of **3** as white needles, which gave positive ninhydrin and negative permanganate reactions: mp 151–152 °C (lit.[11] mp 139–140 °C); NMR (D_2O) δ 2.02–3.55 (br m, 5, CH_2CHCH_2), 4.13 (s, 2, $PhCH_2$), 7.48 (s, 10, C_6H_5); IR (KBr) 3200–1910, 1670–1440 cm^{-1}.

3-[(*N*-Acetyl-*N*-benzylamino)methyl]-1-benzyl-2,5-pyrrolidinedione (6a). A mixture of **3** (41.0 g, 0.12 mol) in 100 mL of Ac_2O was refluxed under a N_2 atmosphere for 45 min. The solution was concentrated under reduced pressure, and the residual solvent was removed by azeotropic distillation with toluene. The resulting orange gum was stirred at room temperature in 100 mL of H_2O for 12 h. The suspension was made basic (pH 10) with 3 N NaOH and extracted with Et_2O. The aqueous layer was acidified (pH 2) with concentrated HCl and extracted with 1 × 75 mL of CH_2Cl_2 and 2 × 75 mL of Et_2O. The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure. The resulting 31.8 g of diacid **5** was refluxed in 60 mL of Ac_2O under a N_2 atmosphere for 10 min, and the solvent removed as described above. The residue was dissolved in CH_2Cl_2, 12.2 g (0.12 mol) of benzylamine was added, and the solution was stirred for 12 h. The solution was concentrated under reduced pressure, the residue was refluxed in 60 mL of Ac_2O under N_2 for 10 min, and the solvent was removed as above. The remaining light brown oil was allowed to stand under Et_2O for 24 h, during which time 18.8 g (47%) of **6a** crystallized as colorless transparent cubes: mp 86–88 °C; TLC ($CHCl_3$–MeOH, 8:2) R_f 0.69; NMR ($CDCl_3$) δ 2.10 (s, 3, CH_3CO), 2.62–3.18 (m, 3, $COCH_2CH$), 3.58–3.80 (br m, 2, $CHCH_2N$), 4.42 (s, 2, $PhCH_2$), 4.58 (s, 2, $PhCH_2$), 6.88–7.25 (s, 5, C_6H_5), 7.32 (s, 5, C_6H_5).

3-[(*N*-Acetyl-*N*-benzylamino)methyl]-1-methyl-2,5-pyrrolidinedione (6b). The crude diacid **5** (21.4 g, 0.07 mol), prepared in the same manner as described for the synthesis of **6a** using 31.3 g (0.09 mol) of **3**, was refluxed in 60 mL of Ac_2O under a N_2 atmosphere for 10 min, and the solvent was removed under reduced pressure with azeotropic distillation by toluene. The residue was dissolved in dry THF containing 5.6 g (0.08 mol) of methylamine hydrochloride and 8.4 g (0.08 mol) of Et_3N and stirred at room temperature while protected from moisture for 36 h. Precipitated Et_3N·HCl was removed by vacuum filtration, and the filtrate was concentrated under reduced pressure. The resulting brown oil was redehydrated for 10 min in refluxing Ac_2O and concentrated as above. The remaining oil was dissolved in $CHCl_3$, washed with 2 × 30 mL of cold saturated $NaHCO_3$, dried ($MgSO_4$), and concentrated under reduced pressure to give 16.6 g of orange oil (crude **6b**). Elution of this oil on a column with $CHCl_3$–MeOH, 95:5, gave 11.8 g (54%) of **6b** as a clear gum: TLC ($CHCl_3$–MeOH, 95:5) R_f 0.36; NMR ($CDCl_3$) δ 2.15 (s, 3, $COCH_3$), 2.53–2.77 (m, 2, $COCH_2$), 2.83–3.30 (m, 1, CH) 2.88 (s, 3, NCH_3), 3.37–4.05 (m, 2, $CHCH_2N$), 4.60 (s, 2, $PhCH_2$), 7.00–7.48 (m, 5, C_6H_5).

3-[(Benzylamino)methyl]-1-benzyl-2,5-pyrrolidinedione Hydrochloride (7a). A solution of 15.1 g (43 mmol) of **6a** in 100 mL of 6 N HCl was refluxed for 2 h and then concentrated under reduced pressure. Residual solvent was removed by azeotropic distillation with absolute EtOH and then toluene to afford a white solid in a yellow oil. The oil was extracted from the mixture with acetone, and the extract was concentrated. The procedure was repeated on the resulting yellow oil to afford a second portion of white solid. The combined solids (12.8 g, 86%) were recrystallized from MeOH to afford 11.8 g of **7a** as white crystals: mp 210–211 °C; NMR (Me_2SO) δ 2.70–3.67 (br m, 5, CH_2CHCH_2), 4.13 (br s, 2, CH_2NCH_2Ph), 4.50 (s, 2, 1-$PhCH_2$) 7.22 (s, 5, C_6H_5), 7.28–7.70 (br m, 5, C_6H_5); IR (KBr) 3450, 2945, 2700, 1770, 1690 cm^{-1}; EIMS, *m/e* (relative intensity) 309 [$(M + 1)^+$, 0.3], 120 (12), 106 (81.4), 91 (100), 77 (3). Anal. ($C_{19}H_{21}N_2O_2Cl$) C, H, N, Cl.

3-[(Benzylamino)methyl]-1-methyl-2,5-pyrrolidinedione Hydrochloride (7b). The crude **6b** (19.6 g) was dissolved in 150 mL of 3 N HCl and refluxed for 18 h. The solution was concentrated under reduced pressure with azeotropic removal of excess solvents by absolute EtOH and toluene. The aqueous phase was concentrated under reduced pressure with azeotropic distillation by absolute EtOH. The resulting slightly purple solid was recrystallized from MeOH to afford 8.7 g of **7b** as white needles: mp 204–205.5 °C; NMR (D_2O) δ 2.63–3.67 (m, 5, CH_2CHCH_2), 2.97 (s, 3, NCH_3), 4.33 (s, 2, $PhCH_2$), 7.50 (s, 5, C_6H_4)[IR (KBr) 3460, 2900, 1778, 1700 cm^{-1}. Anal. ($C_{13}H_{17}N_2O_2Cl$) C, H, N, Cl.

3-(Aminomethyl)-1-benzyl-2,5-pyrrolidinedione Hydrochloride (8a). The salt **7a** (5.4 g, 16 mmol) was dissolved in 60

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mL of warm AcOH and hydrogenolyzed at an initial hydrogen pressure of 60 psi over 1.1 g of 10% Pd/C with external heating (heat lamp). After theoretical pressure drop (8 h), the catalyst was removed by vacuum filtration, and the filtrate concentrated under reduced pressure. Residual AcOH was removed by azeotropic distillation to afford a crude white solid, which was recrystallized from absolute EtOH to yield 3.7 g (93%) of **8a** as white plates: mp 160–161 °C; NMR (D_2O) δ 2.67–3.10 (br m, 2, $COCH_2CH$), 3.23–3.57 (br m, 3, $CHCH_2N$), 4.68 (s, 2, $PhCH_2$), 7.37 (s, 5, C_6H_5); IR (KBr) 3450, 2900, 1770, 1695 cm^{-1}. Anal. ($C_{12}H_{15}N_2O_2Cl$) C, H, N, Cl.

3-(Aminomethyl)-1-methyl-2,5-pyrrolidinedione Hydrochloride (8b). The salt **8b** was prepared by hydrogenolysis of 8.7 g of **7b** (32 mmol) over 1.8 g of 10% Pd/C at 60 psi in the same manner as for the preparation of **8a**. The resulting light green semisolid was crystallized from absolute EtOH and afforded 5.3 g (92%) of **8b** as white needles: mp 168–168.5 °C; NMR (D_2O) δ 2.40–3.03 (m, 2, $COCH_2$), 2.95 (s, 3, NCH_3), 3.17–3.53 (m, 3, $CHCH_2N$); IR (KBr) 3465, 3020, 2930, 1790, 1696 cm^{-1}. Anal. ($C_6H_{11}N_2O_2Cl$) C, H, N, Cl.

3-[(Benzoylamino)methyl]-1-benzyl-2,5-pyrrolidinedione (9a). A suspension of 2.0 g (7.8 mmol) of **8a** in 50 mL of dry THF and 0.8 g (7.8 mmol) of Et_3N was stirred at room temperature for 18 h while protected from moisture. Benzoyl chloride (1.1 g, 7.8 mmol) and an additional 0.8 g of Et_3N were added to the suspension, and stirring was continued for 24 h. The precipitated Et_3N·HCl was removed by vacuum filtration, and the filtrate was concentrated under reduced pressure to afford a light yellow powder. Crystallization from acetone afforded 1.4 g (55%) of **9a** as white needles: mp 142–143 °C; NMR ($CDCl_3$) δ 2.53–3.27 (br m, 3, CH_2CH), 3.37–4.02 (br m, 2, $CHCH_2N$), 4.62 (s, 2, $PhCH_2$), 6.75–7.05 (br s, 1, NH), 7.27 (s, 5, $C_6H_5CH_2$), 7.35–7.77 (br m, 5, C_6H_5CO); IR (KBr) 3270, 1760, 1685, 1620 cm^{-1}. Anal. ($C_{19}H_{18}N_2O_3$) C, H, N.

3-[(Benzoylamino)methyl]-1-methyl-2,5-pyrrolidinedione (9b). The synthesis of **9b** from 2.0 g (11 mmol) of **8b** and 1.6 g (11 mmol) of benzoyl chloride was identical with the preparation of **9a**. The resulting crude light yellow solid was recrystallized from acetone to afford 1.4 g (52%) of **9b** as white plates: mp 126–127.5 °C; NMR ($CDCl_3$) δ 2.57–4.17 (br m, 5, CH_2CHCH_2), 2.95 (s, 3, NCH_3), 7.00–7.97 (br m, 6, C_6H_5CO, NH); IR (KBr) 3280, 1760, 1675, 1615 cm^{-1}. Anal. ($C_{13}H_{14}N_2O_3$) C, H, N.

3-[(Acetylamino)methyl]-1-benzyl-2,5-pyrrolidinedione (9c). The synthesis of **9c** proceeded in the same manner as for **9a** using 3.0 g (0.12 mol) of **8a** and 1.2 g (0.15 mol) of acetyl chloride. The resulting crude yellow solid was recrystallized from $CHCl_3/Et_2O$, 1:1, to yield 2.2 g (71%) of **9c** as white needles: mp 101–102 °C; NMR ($CDCl_3$) δ 1.88 (s, 3, $COCH_3$), 2.50–3.10 (br m, 3, $COCH_2CH$), 3.33–3.73 (br m, 2, $CHCH_2N$), 4.60 (s, 2, $PhCH_2$), 5.93 6.43 (br s, 1, NH), 7.28 (s, 5, C_6H_5); IR (KBr) 3320, 3060, 2925, 1770, 1695, 1640 cm^{-1}. Anal. ($C_{14}H_{16}N_2O_3$) C, H, N.

3-[(*N*-Acetyl-*N*-benzylamino)methyl]-2,5-pyrrolidinedione (6c). A CH_2Cl_2 solution of 4.0 g (14 mmol) of **5** (from 5.2 g, 15 mmol, of **3**) was placed in a pressure bottle, and the solvent was removed under high vacuum. The resulting white glass was dissolved in 2.5 mL of 30% aqueous ammonium hydroxide and 2 mL of absolute EtOH. The volatiles were removed under high vacuum at room temperature to afford an opaque glass. The pressure bottle was filled with N_2, sealed, and heated in an oil bath at 190 °C for 45 min. Excess water was removed from the cooled yellow melt by azeotropic distillation with absolute EtOH. The resulting orange gum was column chromatographed with $CHCl_3$ elution. Early fractions contained a total of 250 mg of **6a** and 200 mg of *N*-benzylacetamide. Later fractions were concentrated under reduced pressure to yield a total of 1.9 g (52%) of **6c** as a clear glass: TLC R_f ($CHCl_3$–MeOH, 9:1) 0.36, R_f (Et_2O–acetone, 2:1) 0.33, R_f (CH_3CN–benzene, 1:2) 0.10; NMR ($CDCl_3$) δ 2.13 (s, 3, $COCH_3$), 2.47–2.80 (br d, 2, $COCH_2CH$), 2.93–3.26 (m, 3, $CHCH_2N$), 4.63 (br s, 2, $PhCH_2$), 7.00–7.43 (br m, 5, C_6H_5), 9.80 (br s, 1, NH).

3-[(Benzylamino)methyl]-2,5-pyrrolidinedione Hydrochloride (7c). A mixture of 1.46 g (3.6 mmol) of **6c** and 75 mL of 1 N HCl was heated at reflux for 6 h. The solution was concentrated under reduced pressure with azeotropic removal of excess solvents by absolute EtOH and toluene, resulting in a fine white powder dispersed in a yellow oil. The oil was dissolved in absolute EtOH, and the ammonium chloride powder was removed by vacuum filtration. The filtrate was concentrated under reduced pressure to a yellow gum. Crystallization from $CHCl_3$–Et_2O–EtOH, 2:2:1, afforded 0.91 g (62%) as a white solid. An analytical sample was obtained by partitioning the solid between $CHCl_3$ and saturated $NaHCO_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and HCl (g) was added, precipitating **7c**, which was recrystallized as white crystals from 1:1 EtOH–Et_2O: mp 170–171 °C; NMR (Me_2SO-d_6) δ 2.67–2.93 (br m, 2, $CHCH_2N$), 3.03–3.67 (br m, 3, $COCH_2CH$), 4.13 (s, 2, $PhCH_2$), 7.20–7.77 (br m, 5, C_6H_5), 9.57–10.10 (br s, 2, NH_2) 11.00–11.38 (br s, 1, CONHCO); IR (KBr) 3300–2400, 1767, 1700 cm^{-1}; EIMS, *m/e* (relative intensity) 219 [$(M + 1)^+$, 9.6], 120 (14.9), 107 (23), 106 (79.4), 91 (100), 79 (10.3), 77 (7.4), 68 (19.2), 51 (7.6). Anal. ($C_{12}H_{15}N_2O_2Cl$) C, H, N.

Methyl 2-Cyanopropanoate (11). The cyano ester was prepared according to the slightly modified procedure of Alexander and Cope.[23] Methyl cyanoacetate (30.0 g, 0.3 mol) and paraformaldehyde (30.0 g, 0.33 mol) were mixed in 100 mL of AcOH and placed over 1 g of 5% Pd/C in a hydrogenation bottle. Pyrrolidine (1 g) was added, and hydrogenation began at an initial hydrogen pressure of 60 psi. After theoretical pressure drop (8 h), the catalyst was removed by vacuum filtration, and the filtrate was dissolved in 400 mL of benzene–Et_2O, 1:1. This solution was washed three times with brine, and the aqueous extracts were then washed with 100 mL of Et_2O. The combined organic phases were washed to neutrality with saturated $NaHCO_3$ while over ice and then washed with brine and dried ($MgSO_4$). The volatiles were removed under reduced pressure to afford 15.3 g (45%) of greenish-yellow oil, which appears to be an 85:15 mixture of **11** and methyl cyanoacetate by NMR analysis: TLC ($CHCl_3$–MeOH 95:5) R_f 0.55 (**14**), 0.43 (methyl cyanoacetate); NMR resonances for **11** ($CDCl_3$) δ 1.55 (d, 3, CH_3, J = 7 Hz), 3.37–3.70 (m, 1, CH), 3.78 (s, 3, $COCH_3$).

Dimethyl 2-Cyano-2-methylsuccinate (12). The crude cyano ester **11** (21.6 g, 0.19 mol) and 10.3 g (0.19 mol) of sodium methoxide were magnetically stirred in 100 mL of dry MeOH for 15 min. Ethyl bromoacetate (34.0 g, 0.19 mol, from a 94% solution) was added dropwise in 20 mL of dry MeOH over 0.5 h, and the resulting mixture was heated at reflux for 12 h. The solution was concentrated under reduced pressure, and the residue was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to give 33.5 g of crude orange oil. Column chromatography with $CHCl_3$ elution gave 28.2 g (80%) of **12** as a light yellow oil: TLC R_f ($CHCl_3$–MeOH, 95:5) 0.54; NMR ($CDCl_3$) δ 1.67 (s, 3, CH_3), 2.78 and 3.12 (q, 2, CH_2, J_{AB} = −17 Hz), 3.72 (s, 3, CO_2CH_3).

Dimethyl 2-[(Acetylamino)methyl]-2-methylsuccinate (13). A mixture or cyano ester **12** (11.7 g, 63 mmol), 7.8 g (95 mmol) of anhydrous powdered sodium acetate, and about 200 mg of Raney nickel W-2 in 100 mL of Ac_2O was hydrogenated at an initial hydrogen pressure of 60 psi and with external heating (heat lamp). After theoretical pressure drop (usually about 32 h), the catalyst was removed by vacuum filtration, and the filtrate was concentrated under reduced pressure with removal of excess solvent by azeotropic distillation with toluene. The residue was dissolved in $CHCl_3$, and the residual sodium acetate was removed by vacuum filtration. The $CHCl_3$ was removed under reduced pressure to afford 14.4 g of **13** as a light yellow oil. Elution of this oil from a column with successive portions of $CHCl_3$, 99:1 $CHCl_3$–MeOH, 98:2 $CHCl_3$–MeOH, and 96:4 $CHCl_3$–MeOH gave 12.9 g (89%) of pure **13** from the final eluant: TLC R_f ($CHCl_3$–MeOH, 95:5) 0.18; NMR ($CDCl_3$) δ 1.25 (s, 3, CCH_3), 1.97 (s, 3, $NCOCH_3$), 2.63 (s, 2, $COCH_2$), 3.45 (d, 2, CH_2N, J = 7 Hz), 3.63 (s, 3, $COOCH_3$), 3.68 (s, 3, $COOCH_3$), 6.53–6.90 (br t, 1, NH, J = 7 Hz).

2-(Aminomethyl)-2-methylsuccinic Acid Hydrochloride (14). A mixture of **13** (5.0 g, 0.02 mol) in 100 mL of 1 N HCl was refluxed for 18 h. The solution was then concentrated under reduced pressure, and residual solvent was removed by azeotropic distillation by absolute EtOH. Impurities were removed from the resulting tan solid by heating in EtOAc–MeOH, 10:1, on a steam bath to afford a white solid. The white solid was recrys-

(23) Alexander, E. R.; Cope, A. C. *J. Am. Chem. Soc.* **1944**, *66*, 886.

tallized from Et_2O–EtOH, 2:1, to afford 3.2 g (75%) of white powder **14**: mp 195–196 °C; NMR (D_2O) δ 1.38 (s, 3, CH_3), 2.75 and 2.95 (q, 2, $COCH_2C$, J_{AB} = −16 Hz), 3.17 and 3.47 (q, 2, CH_2N, $J_{A'B'}$ = −16 Hz); IR (KBr) 3060, 1730, 1690, 1590 cm^{-1}. Anal. ($C_8H_{12}NO_4Cl$) C, H, N.

3-[(Acetylamino)methyl]-3-methyl-1-benzyl-2,5-pyrrolidinedione (15a). The amino acid **17** (2.0 g, 10 mmol) was dissolved in 10 mL of H_2O containing 31 mmol of NaOH and stirred for 5 min while immersed in an ice bath. Ac_2O (1.2 g, 12 mmol) was added, and stirring was continued at room temperature for 20 min. After recooling in an ice-bath, the solution was acidified with concentrated HCl, and the solvents were removed under high vacuum while maintained at room temperature with consecutive azeotropic removal of solvents by CH_3CN, toluene, and absolute EtOH. The residue was triturated with absolute EtOH, and the residual NaCl was removed by vacuum filtration. The filtrate was concentrated under reduced pressure with azeotropic removal of EtOH by benzene. The resulting opaque glassy amide acid was dissolved in 2 mL of EtOH, 1.2 g (11 mmol) of benzylamine was added, and the solution was placed in a pressure bottle. The solvent was removed at high vacuum at room temperature, and the N_2-filled pressure bottled was sealed and heated in an oil bath at 185 °C for 25 min. The resulting melt was eluted from a column with successive portions of $CHCl_3$ and $CHCl_3$–MeOH, 99:1. The fraction eluted with 1% MeOH–$CHCl_3$ was concentrated under reduced pressure, and the resulting gum was crystallized on standing under Et_2O, yielding 2.4 g (87%) of **15a** as white needles, mp 103.5–104.5 °C. An analytical sample was prepared by recrystallization from 1:1 benzene–Et_2O: mp 104–105 °C; TLC R_f ($CHCl_3$-MeOH, 8:2) 0.63; NMR ($CDCl_3$) δ 1.27 (s, 3, CH_3), 1.78 (s, 3, $COCH_3$), 2.45 and 2.78 (q, 2, CH_2C, J_{AB} = −18 Hz), 3.42 [septet, 2, CH_2NH, $J_{A'B'}$ = −14.5 Hz (obtained after decoupling the NH), $J_{A'X}$ = 6.5 Hz], 4.60 (s, 2, $PhCH_2$), 5.90 (br t, 1, NH, $J_{A'X}$ = 6.5 Hz), 7.30 (s, 5, C_6H_5); IR (KBr) 3365, 3060, 3030, 2980, 2960, 1770, 1690, 1545 cm^{-1}. Anal. ($C_{15}H_{18}N_2O_3$) C, H, N.

3-(Aminomethyl)-3-methyl-1-benzyl-2,5-pyrrolidinedione Hydrochloride Hemihydrate (16a). Amide **15a** (0.54 g, 2.0 mmol) was refluxed in 30 mL of 1 N HCl for 13 h and then concentrated under reduced pressure with azeotropic removal of H_2O and AcOH by absolute EtOH and toluene, respectively. The resulting greenish-white solid was recrystallized from EtOH–Et_2O, 1:1, to afford 0.44 g (82%) of **16a** as a white powder: mp 174–175 °C; NMR (D_2O) δ 1.47 (s, 3, CH_3), 2.87 (br s, 2, CH_2CO), 3.32 (s, 2, CH_2N), 4.73 (br s, 6, $PhCH_2$ + NH_3 + $^1/_2H_2O$ − HOD), 7.33 (s, 5, C_6H_5); IR (KBr) 3470, 2980, 1750, 1700 cm^{-1}. Anal. ($C_{13}H_{17}N_2O_2Cl{\cdot}^1/_2H_2O$) C, H, N.

3-[(Acetylamino)methyl]-1,3-dimethyl-2,5-pyrrolidinedione (15b). The amino acid **14** (2.0 g, 10 mmol) was acetylated in the same manner as for **15a**. The resulting opaque glass was dissolved in 2.2 mL of 35% aqueous methylamine and 2 mL of EtOH. Solvents were removed, and the fusion was conducted as for **15a**. The resulting melt was dissolved in EtOH, and the solution concentrated under reduced pressure to give a yellow gum. This gum was dissolved in $CHCl_3$ and eluted from a column with $CHCl_3$–MeOH, 98:2. The solvent was removed from the second fraction to afford 1.75 g (88%) of **15b** as a clear glass: TLC R_f ($CHCl_3$–MeOH, 9:1) 0.35; NMR ($CDCl_3$) δ 1.33 (s, 3, CH_3), 1.98 (s, 3, $COCH_3$), 2.47 and 2.83 (q, 2, $COCH_2$, J_{AB} = −19 Hz), 2.97 (s, 3, NCH_3), 3.45 (d, 2, CH_2N, J = 6 Hz), 6.77–7.10 (br t, 1, NH, J = 6 Hz).

3-(Aminomethyl)-1,3-dimethyl-2,5-pyrrolidinedione Hydrochloride (16b). The amine **16b** was prepared from **15b** (1.0 g, 5 mmol) in the same manner as for **16a**. The resulting glass was crystallized from benzene–Et_2O, 1:1, to afford 0.68 g (71%) of **16b** as white needles: mp 222–223 °C; NMR (D_2O) δ 1.43 (s, 3, CH_3), 2.80 (br s, 2, CH_2CO), 2.97 (s, 3, NCH_3), 3.30 (s, 2, CH_2N); IR (KBr) 3290, 2850, 1770, 1695 cm^{-1}. Anal. ($C_7H_{13}N_2O_2Cl$) C, H, N.

3-(Aminomethyl)-3-methyl-2,5-pyrrolidinedione Hydrochloride (16c). The acid **14** (5.0 g, 25 mmol) was acetylated as for **15a**. The resulting opaque glass was dissolved in 3.9 mL of 30% aqueous ammonia and 5 mL of EtOH. Solvents were removed, and fusion was conducted as for **15a**. The cooled melt was dissolved in EtOH, and the solution was concentrated under reduced pressure to give a light yellow glass. NMR (D_2O) analysis showed the crude glass was a mixture of about 40:60 imide **15c**–pyrrolidone. This crude mixture was dissolved in 100 mL of 1 N HCl and refluxed for 12 h. The solution was concentrated under reduced pressure with azeotropic removal of solvents by EtOH and toluene. The resulting glass was crystallized from EtOH. The light yellow powder was recrystallized from MeOH, affording 1.57 g (35%) of **16c** (based on **14**) as a white powder: mp 228 °C dec; NMR (D_2O) δ 1.48 (s, 3, CH_3), 2.83 (br, s, 2, CH_2CO), 3.37 (s, 2, CH_2N); IR (KBr) 3030 1770, 1715 cm^{-1}. Anal. ($C_6H_{11}N_2O_2Cl$) C, H, N.

1-(Dibenzylamino)-2-propanone (18). A solution of 4.0 g (43 mmol) of 1-chloro-2-propanone, 4.3 g (22 mmol) of dibenzylamine, and 2.63 g (26 mmol) of Et_3N were stirred in 30 mL of THF while protected from moisture for 14 h. The precipitated $Et_3N{\cdot}HCl$ was removed by vacuum filtration, and the filtrate was concentrated under reduced pressure to a brown oil. The oil was dissolved in $CHCl_3$, and this solution was washed with saturated $NaHCO_3$ and brine and dried ($MgSO_4$). The solvent was removed under reduced pressure to afford 4.8 g (87%) of **18** as a light brown oil: TLC R_f ($CHCl_3$–MeOH, 95:5) 0.67; NMR ($CDCl_3$) δ 1.95 (s, 3, $COCH_3$), 3.10 (s, 2, $COCH_2$), 3.58 (s, 4, $PhCH_2$), 7.07–7.40 (m, 10, C_6H_5).

5-[(Dibenzylamino)methyl]-5-methyl-2,4-imidazolidinedione (19). In a 50-mL Erlenmeyer flask were placed 1.40 g (5.5 mmol) of **18**, 0.72 g (11 mmol) of KCN, 2.12 g (22 mmol) of $(NH_4)_2CO_3$, and 10 mL of aqueous EtOH (4:1). The mixture was heated while stirring on a hot plate at 65–70 °C. After 3 h, heating was discontinued, and 10 mL of H_2O was added. After the mixture was cooled to room temperature, the solid was filtered and dried in a heated vacuum desicator, affording 1.39 g (78%). Recrystallization from 95% EtOH afforded 0.82 g of **19** as white crystals: mp 202–204 °C; NMR (Me_2SO-d_6) δ 1.15 (s, 3, CH_3), 2.65 (q, 2, Im-CH_2), 3.31 (s, 1, NH), 3.58 (s, 4, CH_2Ph), 7.26 (s, 10, Ph), 7.38 (s, 1, NH).

5-(Aminomethyl)-5-methyl-2,4-imidazolidinedione (20). Compound **19** (2.46 g 7.6 mmol), 0.21 g of 10% Pd/C, and 100 mL absolute EtOH were placed in a 500-mL Parr hydrogenation bottle and charged to 60 psi with H_2. The mixture was shaken while heating (IR lamp) for 1.5 h. After the mixture was cooled, the catalyst was removed by filtration, and the solvent was evaporated to give 1.08 g (100%) of white solid **20**, mp 186–188 °C. An analytical sample was obtained by recrystallization from 95% EtOH: mp 186.5–188 °C; NMR (Me_2SO-d_6) δ 1.20 (s, 3, CH_3), 2.67 (q, 2, CH_2, J = −13 Hz), 3.90–4.60 (br s, 3, NH_2 and NH), 7.67 (br s, 1, NH). Anal. ($C_5H_9N_3O_2$) C, H, N.

Pharmacological Evaluations. (a) Anticonvulsant Screening Tests. Phase I and phase II testing of the compounds in Tables I and II were performed by the Antiepileptic Drug Development Program by their standard screening protocol.[16,24,25] In phase I studies, the compounds are solubilized in isotonic saline or 30% polyethylene glycol 400 and evaluated at 0.5 and 4 h after intraperitoneal injection in Carworth Farms No. 1 mice against both maximal electroshock and subcutaneous pentylenetetrazole seizure models. Each dose is evaluated in four mice for the ability to prevent tonic hindlimb extension following maximal electroshock and 85 mg/kg subcutaneous pentylenetetrazole. Activity is defined as the lowest dose at which at least one of four animals is protected, provided initial results are confirmed in a second trial. Compounds that showed activity at 100 mg/kg were further examined in phase II for quantification of median effective doses (ED_{50}) and median neurotoxic doses (TD_{50}).

(b) Intracerebroventricular Examination.[19] Male Swiss Webster mice were injected with 10 μL of saline or test compound in saline using a 27-gauge needle fitted with a polyethylene sleeve to expose 4 mm. Accuracy of the injection technique was determined by injection of a saline solution of Methylene blue, followed by autopsy to ascertain difusion of the dye. All experiments were performed on five mice ranging from 25–30 g each. Pentylenetetrazole (85 mg/kg) was administered intraperitoneally

(24) Anticonvulsant Screening Project, Antiepileptic Drug Development Program, *DHEW Publ. (NIH) (U.S.)* **1978**, *(NIH) 78-1093.*

(25) Swinyard, E. A.; Brown, W. C.; Goodman, L. S. *J. Pharmacol. Exp. Ther.* **1952**, *103*, 319.

10 min following administration of the test solution.

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