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Spiro[4.5] and Spiro[4.6] Carboxylic Acids: Cyclic Analogues of Valproic Acid. Synthesis and Anticonvulsant Evaluation[1]

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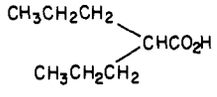
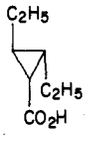
Spiro[4.5]decane-2-carboxylic acid (**12a**), spiro[4.5]decane-2,2-dicarboxylic acid (**11a**), spiro[4.6]undecane-2-carboxylic acid (**12b**), spiro[4.6]undecane-2,2-dicarboxylic acid (**11b**), and spiro[4.6]undecane-2-acetic acid (**13**) were synthesized by an improved method and evaluated for anticonvulsant activity. These analogues were synthesized to evaluate the role of the carboxylic acid group as an essential substituent in valproic acid (di-*n*-propylacetic acid, 1). Carbocyclic spiranes are known to resist metabolic alteration so that any activity elicited by these compounds would be due to the carboxylic acid function and not to any metabolic change. Spiro[4.6]undecane-2-carboxylic acid (**12b**) was the most active analogue tested and the pentylenetetrazol and picrotoxin evaluations of **12b** compared favorably to 1. However, **12b** failed to provide adequate protection against maximal electroshock seizures, bicuculline, or strychnine in mice. Possible reasons for these results are discussed.

Valproic acid (di-*n*-propylacetic acid, 1) was introduced into the United States in 1978 as an anticonvulsant specifically for the treatment of absence (petit mal) seizures.[2]



1

Metabolic alteration of 1 is a significant disadvantage, however.[3] A recent report[4] detailed the synthesis and anticonvulsant evaluation of rigid homologues of 1. This study showed that (±)-(*E*)-2,3-diethylcyclopropanecarboxylic acid (**2**) and dicyclopropylacetic acid (**3**) were as active as 1 against pentylenetetrazol-induced seizures in mice. We herein report our studies on spiro carboxylic acid analogues of 1 as potential anticonvulsants.



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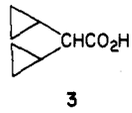

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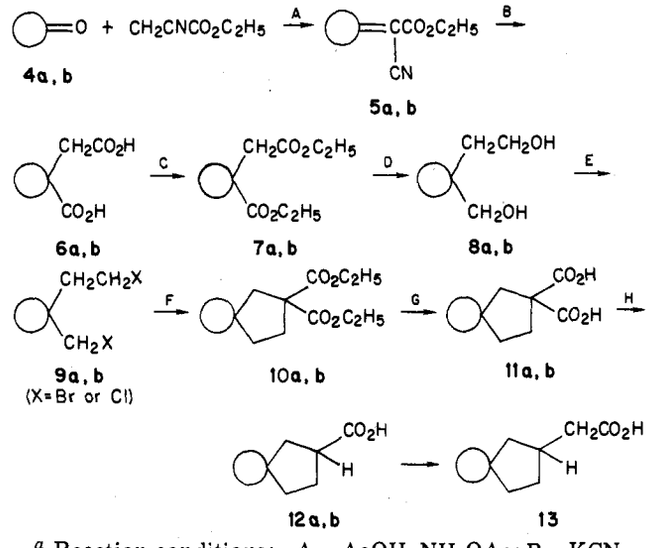
Chemistry. The target compounds were synthesized according to the procedure shown in Scheme I. This synthesis has been detailed in part previously.[5] Starting with the appropriate ketone (cyclohexanone or cycloheptanone, **4**), ethyl cyanoacetate was reacted under Cope conditions[6] and the product, the cycloalkylidenecyanoacetic acid ester **5**, was then reacted with potassium cyanide in a hydroalcoholic solution. After the mixture stood at room temperature for 48 h, the solvents were evaporated, and the residue was treated with hydrochloric acid, refluxed overnight, and upon cooling, the 1-carboxy 1-acetic acid derivative **6** precipitated in nearly pure form.[7]

Scheme I[a]



[a] Reaction conditions: A = AcOH, NH_4OAc; B = KCN, HCl; C = EtOH, H_2SO_4; D = LAH or $NaAlH_2(O(CH_2)_2OCH_3)_2$; E = HBr, H_2SO_4, or $SOCl_2$; F = $CH_2(CO_2Et)_2$, NaOEt; G = KOH, EtOH, HCl; H = Δ; I = $SOCl_2$; CH_2N_2, Et_3N; $C_6H_5CO_2Ag$, Et_3N; NaOH, HCl. Series a = cyclohexanone; series b = cycloheptanone.

Esterification under standard conditions[8] produced the diethyl ester **7**. When **7** was reduced with lithium alu-

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Table I. Phase I Anticonvulsant Testing

compd	dose, mg/kg	MES[a] 0.5 h	MES[a] 4 h	scMet[b] 0.5 h	scMet[b] 4 h	Tox[c] 0.5 h	Tox[c] 4 h	comment
12a	300	1/1[d]	0/1[d]	1/1 (4/4)[g]	0/1[d]	3/4 (1/4)	0/2	
	600	0/0	0/0	1/1	0/1	4/4	0/1	2/4 died in respiratory depression; 2/4 anesthetized
12b	300	1/1[d]	0/1	1/1 (2/4)	0/1	1/4 (0/4)	0/2	
	600	0/0	0/0	1/1	1/1	4/4	1/1	death same as in **12a**
11a	300	0/1	0/1	0/1	0/1	0/4	0/2	
	600	0/1	0/1	1/1 (4/4)	0/1	0/4 (0/4)	2/2	
11b	300	0/1	0/1[e]	1/1 (3/4)	0/1	0/4	0/2	
	600	0/1[d]	0/0[d]	1/1 (4/4)	0/0[d]	3/4 (3/4)	2/2[e]	
13	300	1/1[d]	0/1[d]	1/1 (1/4)	0/1[d]	3/3 (2/4)	0/2	
	600	1/1	0/1	1/1	1/1	4/4	0/2	4/4 anesthetized
12b (Na)[f]	300	0/1	0/1	0/1	0/1	0/4	0/2	
	600	0/1	0/1	1/1	0/0	4/4	2/2	

[a] Maximal electroshock test (number of animals protected/number of animals tested). [b] Subcutaneous pentylenetetrazol test. [c] Toxicity (number of animals exhibiting toxicity/number of animals tested). [d] Toxic at 0.5 h. [e] Toxic at 4 h. [f] Disodium salt of **12b**. [g] Data in parentheses indicates the results of a second trial.

minum hydride under conditions previously reported,[9] the glycol **8** was produced in fair yields. It was found that the inorganic precipitate formed during the workup adsorbed a considerable quantity of **8**. Continuous extraction of the dried inorganic residue with ethyl acetate–acetone (3:1) improved the yields dramatically. Several trials were attempted on the reduction of the diacid **6** with lithium aluminum hydride,[10] but due to their poor solubility in organic solvents, the results were unpredictable. Reduction was also performed with sodium dihydrobis(2-methoxyethoxy)aluminate (Vitride (Hexcel)). The latter reducing agent required a shorter reaction period (2 h vs. 24–48 h) and the workup was less tedious. On bromination of the glycol **8** with fuming hydrobromic acid and sulfuric acid,[9] an unstable product formed, which had to be stored at −15 °C under reduced pressure and reacted within 4 h after isolation. This crude dibromide **9** could, however, be condensed with diethyl malonate to produce the desired 2,2-dicarboethoxy spiranes **10** in good yields. Saponification of the diester in alcoholic potassium hydroxide, followed by acidification of the dipotassium salt, produced the diacid **11**. The diacids were readily decarboxylated to **12** by heating above their melting point and distilling the residue under reduced pressure. The overall yield from cyclohexanone (series a) was 20%, while with cycloheptanone (series b) was 18%. Halogenation of the glycol **8** with a 0.1 molar excess of thionyl chloride in methylene chloride produced a stable dichloride, which, after washing with fresh methylene chloride and evaporation, could be used without further purification in the subsequent steps.[11] This modification resulted in an increased overall yield of 25% and 23%, respectively. Spiro[4.6]undecane-2-acetic acid (**13**) was prepared by the Arndt–Eistert synthesis[12] of **12b**. This reaction was preferred over the earlier work[5] involving the Emmons modification[13] of the Wittig reaction on the respective spiro ketone.

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Table II. Phase II Quantification of Antipentylenetetrazol Activity and Neurotoxicity

compd	scMet ED_{50},[a] mg/kg	TD_{50}, mg/kg	PI[b]
12b	83 (60–105)	193 (176–226)	2.3
11b	194 (168–258)	275 (225–326)	1.4
valproic acid[c]	149 (123–177)	426 (369–450)	2.9

[a] Measured at time of peak effect, 0.5 h. Values in parentheses are 95% confidence intervals determined by probit analysis. [b] Protective index (TD_{50}/ED_{50}). [c] Values from ref 16.

Table III. Phase V Quantification of Antipicrotoxin Activity and Neurotoxicity

compd	scPic ED_{50},[a] mg/kg	TD_{50}, mg/kg	PI
12b	167 (137–195)	193 (176–226)	1.2
valproic acid[b]	387 (341–444)	426 (369–450)	1.1

[a] Subcutaneous picrotoxin (3.2 mg/kg). [b] Values from ref 16.

Biological Results and Discussion

Preliminary pharmacological testing of compounds **11a,b**, **12a,b**, and **13** were performed by the Antiepileptic Drug Development Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke. Phase I analysis in mice is shown in Table I. The three tests were maximal electroshock seizure (MES), subcutaneous pentylenetetrazol (scMet), and neurologic toxicity (Tox). All compounds, including the disodium salt of **12b**, displayed little activity against seizures induced by MES. The latter compound was submitted for testing due to the high lipophilicity exhibited by **12a** and **12b**.[14] This compound, however, was slightly soluble in water and thus did not provide the anticipated distribution.[14] Protection against pentylenetetrazol-induced seizures was shown for **11b**, **12a**, and **12b** at 300 mg/kg at 0.5 h and by **11a** at 600 mg/kg. The low order of toxicity of **11a**, **11b**, and **12b** at 300 mg/kg at 0.5 h prompted further evaluation. Phase II results on the quantification against scMet for **11b** and **12b** are shown in Table II. These data were provided by the Antiepileptic Drug Development (ADD) Program. Valproic acid is shown for comparison. The ED_{50} for **12b** is lower than for valproic acid with a protective index comparable to the latter; thus **12b** was evaluated in phase V quantification against bicuculline, picrotoxin, pentylenetetrazol, and strychnine. Data for picrotoxin are shown in Table III. Valproic acid is shown for comparison. As with scMet, **12b** had a lower ED_{50} and a comparable protective index in the picrotoxin test. Bicuculline and strychnine data were disappointing, as no protection was shown in doses up to

(14) Zalucky, T. B., unpublished data.

Table IV. Anticonvulsant Testing against Bicuculline-Induced Seizures[a]

pretreatment	pretreatment time, min	dose, mg/kg, sc	av onset,[b] min (no. of mice protected/no. of mice tested) clonic seizure[c]	tonic seizure[d]	death
PEG 30%	15		7 ± 2 (0/8)	11 ± 4 (0/8)	13 ± 4 (0/8)
PEG 30%	30		6 ± 2 (0/4)	9 ± 2 (0/4)	9 ± 2 (0/4)
valproic acid	15	360	9 ± 2 (0/3)	11 (2/3)	15 ± 2 (1/3)
	15	400	15 ± 8 (1/4)	17 ± 11 (2/4)	18 ± 11 (2/4)
11b	30	300	9 ± 4 (0/4)	12 ± 3 (1/4)	13 ± 5 (1/4)
12a	30	200	8 ± 4 (0/4)	11 ± 3 (0/4)	12 ± 3 (0/4)
12b	15	150	7 ± 2 (0/4)	10 ± 3 (0/4)	10 ± 2 (0/4)
12b	30	150	8 ± 3 (0/4)	13 ± 6 (0/4)	14 ± 6 (0/4)

[a] Bicuculline (3.75 mg/kg) administered subcutaneously. [b] Values are mean ±SD. [c] Indicates at least one 5-s episode of clonic spasms. [d] Indicates a period of hindlimb flexion followed by hindlimb extension.

Table V. Anticonvulsant Testing against Picrotoxin-Induced Seizures[a]

pretreatment	pretreatment time, min	dose, mg/kg, sc	av onset (min)[b] of clonic seizure[c]	no. of mice protected/no. of mice tested
PEG 30%	15		13 ± 1	0/4
valproic acid	15	400	16 ± 4	1/4
12b	15	180	21 ± 4	0/4

[a] Picrotoxin (4.0 mg/kg) administered subcutaneously. [b] Values are mean ±SD. [c] Indicates at least one 5-s episode of clonic spasms.

400 mg/kg. The subcutaneous bicuculline and subcutaneous picrotoxin tests were repeated in the laboratory with **11b**, **12a**, **12b**, and valproic acid. Results are shown in Tables IV and V. Bicuculline was administered in a dose of 3.75 mg/kg whereas the picrotoxin dose was 4.0 mg/kg. It should be noted that both bicuculline and picrotoxin dosages differed from the ADD Program protocol.[15,17] Under the conditions used in this laboratory, **11b** protected one out of four mice from bicuculline-induced tonic seizures and death. Neither **12a** nor **12b** demonstrated any activity when evaluated against bicuculline, and **12b** also failed to provide protection against picrotoxin-induced convulsions. Valproic acid did provide some protection at both the 360 and 400 mg/kg doses against bicuculline-induced seizures and at the 400 mg/kg dose against seizures induced by picrotoxin. The ED_{50} values for valproic acid protection against bicuculline and picrotoxin induced seizures in mice were previously reported to be 360 and 387 mg/kg, respectively.[16] The convulsant doses used to determine the ED_{50} values were somewhat lower than those used in this laboratory, however: 2.7 mg/kg for bicuculline and 3.2 mg/kg for picrotoxin. The effectiveness of **12b** against bicuculline and picrotoxin would have added much to the mechanism of action of valproic acid as these convulsants are considered antagonists of γ-aminobutyric acid (GABA),[19,20] a major inhibitory neurotransmitter in the brain.[21] Valproic acid has been shown to increase GABA levels in the brain in animals.[22] Whether it acts reversibly is questioned.[23]

Recently,[24] the 2-ene and 4-ene forms of valproic acid were found in the brain of rats infused with valproic acid. These metabolites were found to be 50 times as potent as the parent drug against pentylenenetetrazol-induced seizures. Since **12b** is not significantly metabolized,[14] its mode of action must be due to the intact carboxylic acid moiety. It was shown that valproic acid bears a steric resemblance to GABA.[25] The resemblance of **12b** to valproic acid is likewise apparent. The rigid orientation of the spiro rings in **12b**, however, allow little torsional vibration within the molecule. This limited orientation may be used as a biologic probe in determining the active conformation of valproic acid. More importantly, the absence of a biotransformation mechanism for the carbocyclic spiranes would provide information on the reversible nature of valproic acid. The kinetics of **12b** will be reported subsequently.

The mechanism of action of **12b** in protecting the animals from the convulsant action of pentylenetetrazol was investigated. A theory has been proposed that anticonvulsants may act on voltage-dependent channels regulating neurotransmitter release.[26] Thus **11b**, **12a**, **12b**, and valproic acid were submitted for testing.[27] None of the compounds displayed any inhibitory or stimulatory effects within the range 10^{-8} to 10^{-4} M.[29]

In summary, **12b**, the most active of a series of spiro carboxylic acids is effective against pentylenetetrazol-induced seizures. This seizure protection would indicate effectiveness against absence (petit mal) seizures.[29] In comparing **12b** to **13**, it can be stated that increasing the distance of the carboxylic acid group from the ring by a

(15) The ADD Program used 2.70 and 3.2 mg/kg for the bicuculline and picrotoxin evaluations, respectively.
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(29) [^{3}H]Nimodipine binding assays were conducted through the Rudolf Buchheim Institute for Pharmacology, Justus Liebig University, Giessen, FRG.

methylene group decreases pentylenetetrazol inhibition and increases toxicity. A general structure–activity correlation would have to await the synthesis and evaluation of a considerable number of spiro carboxylic acid analogues.

Experimental Section

Chemistry. Melting points were obtained with a Thomas-Hoover capillary melting point apparatus and are uncorrected. Observed boiling points were also uncorrected. IR spectra were obtained on a Perkin-Elmer 1330 infrared spectrophotometer either as KBr pellets or neat. ^{1}H NMR spectra were determined on a 60-MHz Varian EM-360A spectrometer with Me_4Si as the internal reference. Drying of organic extracts was performed by storage overnight over sodium sulfate. Elemental analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, NY. Where analyses are indicated only by the symbols of the elements, analytical results for the elements were within 0.4% of the theoretical values.

Ethyl α-Cycloheptylidene-α-cyanoacetate (5b). The general procedure of Cope and co-workers[6] was followed with use 1.2 mol of **4b**, 1.0 mol of ethyl cyanoacetate, 7.7 g NH_4OAc, and 12 g of HOAc in 150 mL of benzene. After refluxing for 8 h, the mixture was cooled to room temperature, and washed with H_2O (100 mL) and saturated NaCl (100 mL), and the combined washings were extracted with 150 mL of Et_2O. The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and distilled: bp 108–110 °C (0.45 mm) (lit.[30] bp 160 °C (12 mm)); yield, 177 g (85%), as a light yellow viscous oil; NMR ($CDCl_3$) δ 1.3 (t, 3 H, CH_3, J = 10.5 Hz), 1.6 (br s, 8 H, C_3–C_6 protons on ring), 2.8 (m, 4 H, C_2, C_7 protons on ring), 4.2 (q, 2 H, CH_2, J = 10.5 Hz); IR (neat) 2210, 1720 cm^{-1}. Anal. ($C_{12}H_{17}NO_2$) C, H, N.

1-Carboxycycloheptane-1-acetic Acid (6b). The general procedure of Vogel[7] was followed with use of 0.4 mol of **5b** in 300 mL of EtOH and 0.8 mol of KCN in 200 mL of H_2O. After mixing of the two solutions, the clear yellow mixture was stoppered and allowed to stand at room temperature for 2 days. After the solvents were removed under reduced pressure, the residue was reacted with 500 mL of HCl, added over 1 h with stirring. The suspension was refluxed for 16 h, and on cooling to room temperature, the acid **6b** separated. It was filtered, washed thoroughly with cold water (500 mL), and dried. All of the washings and the remaining HCl were combined, boiled to half its volume, and refrigerated overnight. The crude acid thus obtained was separated and washed as before and the total recrystallized from H_2O: mp 160–162 °C (lit.[30] mp 159 °C); yield, 66 g (82%), as white needles; NMR (Me_2CO-d_6) δ 1.5 (br s, 8 H, C_3–C_6 protons on ring), 2.0 (br s, 4 H, C_2, C_7 protons on ring), 2.5 (s, 2 H, CH_2CO_2), 8.5 (br, 2 H, CO_2H); IR (KBr) 3000, 1710 cm^{-1}.

Ethyl 1-(Ethoxycarbonyl)cycloheptane-1-acetate (7b). The ester was prepared with use of **6b** (104 g, 0.52 mol), 650 mL of absolute EtOH, 325 mL of benzene, and 45 g of H_2SO_4. After stirring and refluxing for 24–36 h, the mixture was cooled to room temperature and washed with H_2O (3 × 200 mL) and saturated $KHCO_3$ (2 × 200 mL). The aqueous extract was extracted with Et_2O (2 × 200 mL) and the Et_2O separated and washed with $KHCO_3$ (2 × 100 mL). The combined organic layers were dried (Na_2SO_4), concentrated under reduced pressure, and distilled, bp 113–114 °C (0.7 mm), as a clear mobile oil: yield, 110.5 g (83%); NMR ($CDCl_3$) δ 1.2 (t, 6 H, 2 CH_3, J = 7.2 Hz), 1.5 (br s, 8 H, C_3–C_6 protons on ring), 2.0 (br m, 4 H, C_2, C_7 protons on ring), 2.6 (s, 2 H, CH_2CO_2), 4.13 (m, (two overlapping quartets), 4 H, 2 CH_2, J = 7.2 Hz); IR (neat) 1720 cm^{-1}. Anal. ($C_{14}H_{24}O_4$) C, H.

1-(Hydroxymethyl)-1-(β-hydroxyethyl)cycloheptane (8b). Method A. To LAH, 45 g (1.19 mol) in 1 L of dry Et_2O, was added **7b** (71 g, 0.28 mol) in dry THF (300 mL) over 90 min with vigorous stirring. After the addition, the mixture was refluxed for 24–48 h, cooled, and decomposed with H_2O, and after filtration of the inorganic residue, the organic solvents were dried (Na_2SO_4). The residue was dried at 80 °C overnight, triturated into a fine powder, and transferred to a Soxhlet apparatus where it was extracted continuously with a mixture of EtOAc–Me_2CO (3:1) for 24 h. The solvent mixture was combined with the organic layer, concentrated under reduced pressure, and distilled: bp 125–129 °C (0.25 mm); yield, 37.5 g (59%) of a viscous, pale yellow oil that solidified on standing: mp 56–58 °C (MeOH) as clear waxy crystals; NMR ($CDCl_3$) δ 1.4 (br s, 14 H, C_2–C_7 protons on ring + CH_2 (triplet massed)), 3.3 (s, 2 H, CH_2), 3.7 (t, 2 H, CH_2, J = 10.5 Hz), 4.4 (s, 2 H, OH (exchanged with D_2O)); IR (neat) 3290 cm^{-1}. Anal. ($C_{10}H_{20}O_2$) C, H.

Method B. To a vigorously stirred solution of sodium bis(2-methoxyethoxy)aluminate (Vitride, 70% solution in toluene), 124 mL (0.44 mol), in 300 mL of toluene was added **7b** (51.2 g, 0.2 mol) over 20 min. The mixture was refluxed for 2 h and after cooling was slowly added to 900 mL of 6 N HCl, while the mixture was stirred constantly and the temperature maintained below 50 °C with external cooling. After all the salts had dissolved, the mixture was separated and the organic layer washed with H_2O (3 × 100 mL) and dried (Na_2SO_4). The aqueous washings were extracted first with toluene (100 mL) and separated and then with Et_2O (100 mL) and combined with the organic layer. Concentration, under reduced pressure, and distillation of the residue produced **8b** (bp 134–139.5 °C (0.35 mm)), yield 19 g (56%).

1-(Chloromethyl)-1-(β-chloroethyl)cycloheptane (9b, R = Cl). A solution of **8b** (23.8 g, 0.14 mol) in CH_2Cl_2 (150 mL) was added to a stirred solution of $SOCl_2$ (24 mL, 0.32 mol) in CH_2Cl_2 (300 mL). The mixture was refluxed overnight. The solvent and excess $SOCl_2$ were removed under reduced pressure, and fresh CH_2Cl_2 (3 × 200 mL) was added and the mixture evaporated. IR spectra showed no absorption between 3000 and 3500 cm^{-1}. Yield: 24.6 g (84%). An analytical sample was prepared, bp 116–118 °C (0.45 mm), as a clear liquid that darkens on standing. It must be stored at −15 °C under reduced pressure until use. Anal. ($C_{10}H_{18}Cl_2$) C, H, Cl.

1-(Bromomethyl)-1-(β-bromoethyl)cycloheptane (9b, R = Br). To 48.8 g (0.29 mol) of **8b** in 600 mL of HBr (48%) was added 300 mL of H_2SO_4 with stirring and cooling to maintain a temperature not exceeding 15 °C. After the addition, the mixture was heated on a steam bath for 24 h. After cooling to room temperature, the solid residue was separated by vacuum filtration and thoroughly extracted with Me_2CO (350 mL) and Et_2O (500 mL). The acid layer was poured into a beaker containing ice and extracted with Et_2O (3 × 500 mL). The Et_2O was then washed successively with H_2O (2 × 200 mL), saturated $KHCO_3$ (3 × 100 mL), and saturated NaCl (3 × 100 mL), combined with the Me_2CO–Et_2O extract, and dried (Na_2SO_4). The remaining undissolved solid was treated with H_2O (500 mL) and excess solid $KHCO_3$ and the mixture allowed to stand at room temperature overnight. The mixture was separated by vacuum filtration, the aqueous layer extracted with Et_2O (200 mL), and the solid macerated with Me_2CO (200 mL) and Et_2O (250 mL). The organic solvents were combined and concentrated under reduced pressure to yield a mobile, dark brown liquid which did not distill. It gave a single spot on TLC ($CHCl_3$–MeOH, 2:1), R_f 0.79. It was stored at −15 °C under reduced pressure and used within 4 h.

2,2-Dicarboethoxyspiro[4.6]undecane (10b). To 200 mL of absolute EtOH was added 7.8 g (0.34 mol) of Na with stirring. Gentle warming shortens the reaction time. Diethyl malonate (27.0 g, 0.17 mol) was added at once and the mixture was refluxed for 15 min and the crude halide **9b** (0.15 mol) was added as rapidly as possible and the mixture refluxed for 24 h. The suspension was cooled to room temperature, acidified with 10% HCl (125 mL), diluted with H_2O (100 mL), and extracted with Et_2O (3 × 300 mL). The combined Et_2O extracts were washed with H_2O (100 mL) and saturated NaCl (100 mL) and dried (Na_2SO_4). Evaporation of the solvent under reduced pressure and distillation at 9.5 mm produced two fractions: fraction 1, boiling point below 150 °C; fraction 2, boiling point above 150 °C. Fraction 2 was redistilled and produced **10b**: bp 116–124 °C (0.35 mm); yield, 21.6 g (48%), as a clear liquid; NMR ($CDCl_3$) δ 1.2 (t, 6 H, 2 CH_3, J = 7.2 Hz), 1.5 (br s, 14 H, protons on seven-membered ring + CH_2 on C_4), 2.1 (s, 2 H, CH_2 on C_1), 2.2 (t, 2 H, CH_2 on C_3 (overlaps with singlet at 2.1), 4.2 (q, 4 H, 2 CH_2, J = 7.2 Hz); IR (neat) 1730 cm^{-1}. Anal. ($C_{17}H_{28}O_4$) C, H.

Spiro[4.6]undecane-2,2-dicarboxylic Acid (11b). A solution of KOH (25.2 g, 0.45 mol) in EtOH (280 mL) was heated to reflux and **10b** (25.2 g, 0.085 mol) added with stirring while a gentle reflux was maintained. The mixture was heated an additional 2 h, and

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on cooling, the dipotassium salt precipitated. The precipitate was collected by vacuum filtration, washed with absolute EtOH, and dried. The salt was dissolved in H_2O, decolorized with C, heated to boiling, and filtered into an ice-cold stirred 10% HCl solution. After filtration, the filtrate was refrigerated overnight to yield an additional quantity of crude **11b**. The EtOH filtrate and washings provided an additional 2 g of crude **11b** after workup. The crude acid was recrystallized from MeOH to provide **11b**, 15.9 g (78%); mp 181–181.5 °C dec (gas evolution), as white needles: NMR (Me_2CO-d_6) δ 1.5 (br s, 14 H, protons on seven-membered ring + CH_2 on C_4), 2.1 (m, 4 H, CH_2 on C_1 and C_3 overlap), 7.6 (br, 2 H, CO_2H); IR (KBr) 3300–3020, 1680 cm^{-1}. Anal. ($C_{13}H_{20}O_4$) C, H.

Spiro[4.6]undecane-2-carboxylic Acid (12b). The dicarboxylic acid **11b** (10 g, 0.04 mol) was gradually heated in an oil bath until the temperature reached 200 °C, where it was maintained for 1 h. The residue was distilled to yield **12b**: bp 105–110 °C (0.35 mm), yield, 8.2 g (85%) as a clear oil; NMR ($CDCl_3$) δ 1.4 (s, 14 H, protons on seven-membered ring + CH_2 on C_4), 1.8 (m, 4 H, CH_2 on C_1 and C_3), 2.86 (quintet, 1 H, $CHCO_2$), 11.31 (s, 1 H, CO_2H); IR (neat) 3480–2990, 1695 cm^{-1}. Anal. ($C_{12}H_{20}O_2$) C, H.

Spiro[4.6]undecane-2-acetic Acid (13). A solution of $SOCl_2$ (7.8 mL, 0.11 mol) in 60 mL of CH_2Cl_2 was added to **12b** (5 g, 0.026 mol) in 150 mL of CH_2Cl_2 and the mixture stirred and refluxed for 24 h. Evaporation of the solvents under reduced pressure and washing with CH_2Cl_2 (2 × 200 mL) afforded the crude acid chloride, which was used without purification. A solution of the acid chloride in 150 mL of dry THF was added dropwise over 30 min at 0 °C to a stirred solution of 4.4 mL (0.031 mol) of Et_3N and CH_2N_2 (prepared from 9.7 g (0.045 mol) of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (Diazald[31])) in 150 mL anhydrous Et_2O. Stirring was continued for 3 h at 0 °C under N_2. The suspension was filtered and the precipitate washed with THF (2 × 50 mL) and Et_2O (2 × 50 mL). The solvents were concentrated under reduced pressure, and the residue was chromatographed on a dry silica gel column with benzene–$CHCl_3$ (1:1) to afford the diazo ketone, a light green oil: yield, 4.4 g (76%); IR (neat) 2095, 1630 cm^{-1}. The crude diazo ketone, 4.0 g (0.018 mol) in 100 mL of absolute EtOH, was refluxed and treated with a 10% solution of silver benzoate in Et_3N (0.5 mL) under N_2. A total of 15 mL was slowly added over 15 min. The mixture was refluxed an additional 1 h, cooled, and filtered through Celite. The filtrate was concentrated under reduced pressure, the residue taken up with Et_2O (100 mL), and the organic layer washed with 10% Na_2CO_3 (100 mL), saturated NaCl (2 × 50 mL), and dried (Na_2SO_4). Evaporation yielded the crude ethyl spiro[4.6]undecane-2-acetate, 2.65 g (74%), which was saponified with NaOH (5.5 g, 0.14 mol) in 55 mL of MeOH and 110 mL of H_2O for 4 h. Evaporation of the MeOH and acidification with cold 10% HCl was followed by extraction with Et_2O (2 × 200 mL) and drying (Na_2SO_4). The product, after evaporation under reduced pressure and distillation (bp 160–163 °C (0.45 mm)), yield 1.82 g (64%), was a light yellow oil: NMR ($CDCl_3$) δ 1.50 (br s, 18 H, protons on seven membered ring + CH_2 on C_1, C_3, and C_4), 2.3 (m, 3 H, $CHCH_2CO_2$), 11.0 (s, 1 H, CO_2H); IR (Neat) 3000, 1690 cm^{-1}. Anal. ($C_{13}H_{22}O_2$) C, H.

Pharmacology. Initial evaluation for anticonvulsant activity was done by the Antiepileptic Drug Development Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke and included phases I, II, and V testing procedures, which have previously been described.[32] These tests were performed in male Carworth Farms no. 1 mice. Phase I of the evaluation included three tests: maximal electroshock (MES), subcutaneous pentylenetetrazol (scMet), and the rotorod test for neurological toxicity (Tox). Compounds were suspended in 30% polyethylene glycol 400 and were administered by intraperitoneal injection at four dosage levels (30, 100, 300, and 600 mg/kg) at 30 min and 4 h before testing. Phase II testing quantitated the anticonvulsant activity and neurotoxicity by determining the median effective dose (ED_{50}) and median toxic dose (TD_{50}) for those compounds which protected in the MES and scMet tests. For the determination of the ED_{50} or TD_{50}, groups of 6–12 mice were given a range of doses of the test compounds until at least three points were established in the range of 10–90% seizure protection or minimal neurotoxicity. From a plot of the data, the respective ED_{50}, TD_{50}, and 95% confidence intervals were calculated by the method of Litchfield and Wilcoxon.[33] Phase V of the testing measured the ability of the compounds to provide protection against seizures induced by subcutaneous injection of the CD_{97} of the following convulsant agents: Met (85 mg/kg), bicuculline (2.7 mg/kg), picrotoxin (3.15 mg/kg), and strychnine (1.2 mg/kg). As in phase II, the ED_{50} values were determined at the time of peak effect.

On the basis of the data obtained from the initial screening, additional tests were performed in this laboratory on compounds **11b**, **12a**, **12b**, and valproic acid with use of Sprague–Dawley CF1 mice. These compounds were evaluated for their ability to protect against bicuculline- and picrotoxin-induced (3.75 and 4.0 mg/kg, respectively) seizures at their time of peak effect. This dose of bicuculline produces clonic and tonic seizures and death in 100% of the control animals tested. Picrotoxin at 4.0 mg/kg produces clonic convulsions in 100% of the control mice. Control animals in all phases of testing were injected with the solvent, 30% polyethylene glycol 400.

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