Synthesis and Anticonvulsant Evaluation of Some New 2-Benzylsuccinimides

R. RICHARD GOEHRING, THOMAS D. GREENWOOD, JYOTHI S. PISIPATI, AND JAMES F. WOLFE[x]

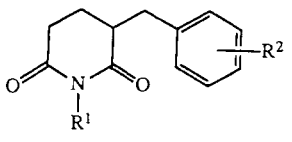
Received March 15, 1990, from the *Department of Chemistry, and The Harvey W. Peters Research Center for the Study of Parkinson's Disease and Disorders of the Central Nervous System, Virginia Polytechnic Institute and State University, Blacksburg, VA 24016.* Accepted for publication September 27, 1990.

Abstract □ A series of 2-benzylsuccinimides (**4a–f**) were prepared for evaluation as potential anticonvulsants. Primary (Phase I) screening of these compounds indicated that succinimides **4d** and **4e**, containing lipophilic ($+\pi$), electron-withdrawing ($+\sigma$) phenyl substituents, were the most effective in controlling seizures induced by maximal electroshock (MES) and subcutaneous pentylenetetrazol (scMet). Compounds **4a**, **4c**, and **4d** showed activity against scMet-induced seizures equal to that of their 2-phenylsuccinimide analogues and were somewhat more effective in the MES test. In quantitative (Phase II) testing, when administered ip in mice, **4d** and **4e** both demonstrated anticonvulsant potency superior to that of the prototype drug (ethosuximide) by the MES and scMet assays. However, they also exhibited greater neurotoxicity than ethosuximide in the rotorod test.

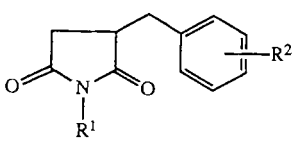
We recently reported[1] the preparation and anticonvulsant activity of a series of 2-benzylglutarimides (**1**). Several compounds of type **1** having an electron withdrawing ($\sigma+$) phenyl substituent (R_2) showed good protection against seizures induced by maximal electroshock (MES) and subcutaneous pentylenetetrazol (scMet). In Phase I screening, a total of seven compounds demonstrated anti-scMet activity at doses of 100 mg/kg or less. Ultimately, 2-(4-chlorobenzyl)glutarimide (**1**, R_1 = H, R_2 = 4-Cl) was selected as the most attractive candidate drug, having ED_{50} values of 136.8 and 72.76 mg/kg in the MES and scMet tests, respectively, combined with low neurotoxicity (TD_{50} = 1224 mg/kg).

In light of these promising results and the well-documented efficacy of certain succinimides in controlling seizures,[2,3] it appeared to us that 2-benzylsuccinimide analogues (**2**) of glutarimide **1** might also possess considerable potential as anticonvulsants. This prediction was supported by a report by Babiyan et al.[4] that *N*-methyl-2(4-*n*-butoxybenzyl)succinimide (**2**, R_1 = CH_3, R_2 = 4-*n*-BuO) exhibited anti-scMet activity similar to that of phensuximide and methsuximide.

Miller and Long[5] also found anticonvulsant activity in a series of 2-phenylsuccinimides in which the nature of the phenyl substituent had a profound effect on anticonvulsant efficacy. It was, therefore, of interest to determine if a similar substituent–activity correlation would be observed for the analogous 2-benzylsuccinimides and to contrast the relative activities between like members of the two series. In this paper, we describe the synthesis of some new 2-benzylsuccinimides (**2**) and the evaluation of their anticonvulsant properties.



1



2

Experimental Section

Chemistry—Melting points were obtained on a Thomas Hoover melting point apparatus and were uncorrected. Elemental analyses were performed in our analytical services department under the direction of T. E. Glass using a Perkin-Elmer 240 C, H, and N analyzer or by Galbraith Laboratories, Knoxville, TN (see Table I). Anhydrous liquid NH_3 (Matheson) was used directly from the tank since distillation from sodium was shown not to influence the outcome of the reactions. The ^1H NMR spectra were recorded on a Varian EM-390 spectrometer with Me_4Si as the internal reference. The IR spectra were determined on samples as 5% $CHCl_3$ solutions using a Perkin-Elmer 710B IR spectrophotometer.

General Procedure for the Preparation of 2-Benzylsuccinimides (4)—The disodium salt of succinimide (**3**) was prepared using a modification of the procedure of Bryant and Hauser.[6] A 1-L, three-necked, round-bottom flask equipped with a pressure equalizing addition funnel, a dry-ice:acetone condenser, and a metal stirring bar was continuously kept under a flow of dry nitrogen while 500 mL of anhydrous liquid NH_3 was added. Small pieces of sodium metal (5.06 g, 0.22 mol) were added along with a catalytic amount of ferric nitrate nonahydrate. When the blue color was discharged, powdered succinimide (9.90 g, 0.10 mol) was added and the resulting yellow suspension was stirred for 30 min. A solution of 4-methyoxybenzyl chloride (17.20 g, 0.11 mol) in 30 mL of anhydrous ether was added rapidly. After stirring for 1 h, the reaction was quenched by pouring onto solid NH_4Cl (16.05 g, 0.30 mol) contained in a 1-L beaker. Ether (200 mL) was added slowly (CAUTION—rapid addition of ether may cause superheating of liquid NH_3 causing it to erupt) and the NH_3 was allowed to evaporate. A mixture of 200 mL of ice and 25 mL of concentrated HCl was added and stirred until the ice melted. The ethereal layer was separated and the aqueous layer, including some suspended solid, was extracted with ether (3 × 100 mL). The combined ethereal solutions were extracted with 5% aqueous NaOH (4 × 100 mL). The combined alkaline extracts were cooled in an ice bath and acidified to pH 1 with concentrated HCl. The oil which separated was dissolved in ether. The ethereal solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to give the crude product. Following recrystallization from EtOAc:heptane, **4c** was obtained as white needles, mp 109–111 °C; ^1H NMR ($CDCl_3$): δ 2.27–3.37 (m, 5H, aliphatic), 3.80 (s, 3H, OCH_3), 6.97 (q, 4H, aromatic), 7.89 (br s, 1H, NH); IR (5% solution in $CHCl_3$): 3390 (NH), 1785 (C=O), and 1718 (C=O) cm^{-1}.

Anal.—Calc. for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.93; N, 6.39. Found: C, 65.71; H, 5.84; N, 6.33.

Pharmacology—Pharmacological testing was performed by the Antiepileptic Drug Development Program, Epilepsy Branch, Neurological Disorders Program, National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) using procedures which have been previously described.[7] All tests were conducted on male Carworth Farms #1 mice weighing 18–25 g. Test compounds were administered in 30% polyethylene glycol 400 by ip injection. In Phase I screening (Table II), each compound was given in four dosage levels (30, 100, 300, and 600 mg/kg). Anticonvulsant activity and neurotoxicity were assessed 30 min and 4 h after administration. Phase II quantification of these pharmacological parameters (Table

0022-3549/91/0800-0790$01.00/0

Table I—Analyses of New Compounds

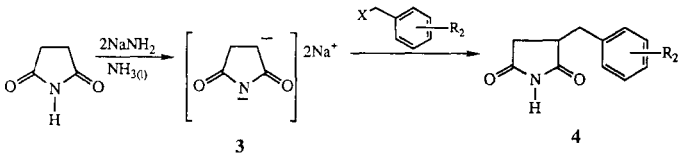
Compound	Formula	Anal. Calc. (Found)
4b	$C_{12}H_{13}NO_2$	C, 70.94 (70.93); H, 6.40 (6.47); N, 6.90 (6.85)
4c	$C_{12}H_{13}NO_3$	C, 65.75 (65.71); H, 5.93 (5.84); N, 6.39 (6.33)
4d	$C_{11}H_{10}ClNO_2$	C, 59.06 (59.34); H, 4.47 (4.37); N, 6.26 (6.09)
4e	$C_{11}H_9Cl_2NO_2$	C, 51.19 (51.17); H, 3.51 (3.34); N, 5.43 (5.18)
4f	$C_{14}H_{19}SiNO_2$	C, 64.33 (64.04); H, 7.33 (7.34); N, 5.36 (5.36)

Table II—Phase I Pharmacological Testing Data for 4a–f[a]

Compound	MES[b]		scMet[c]		Toxicity[d]	
	0.5 h	4.0 h	0.5 h	4.0 h	0.5 h	4.0 h
4a	++(1/1)	—	++(4/4)	—	++(4/4)	—
4b	+(1/1)	—	—	—	+(2/4)	—
4c	+(1/1)	—	++(2/4)	—	+(4/4)	—
4d	+++(1/1)	++(1/1)	+++(3/4)	++(1/1)	+(4/4)	+(2/2)
4e	++(1/1)	++(1/1)	+++(2/4)	+(1/1)	+(2/4)	+(2/2)
4f[e]	++(1/1)	++(1/1)	++(3/4)	—	++(3/4)	+(1/2)

[a] +++, ++, and + denote activity or toxicity at 100, 300, and 600 mg/kg, respectively, and — denotes no activity or toxicity up to 600 mg/kg. [b] Maximal electroshock seizure test (number of animals protected/number of animals tested). [c] Subcutaneous pentylenetetrazol test. [d] Neurological toxicity (number of animals toxic/number of animals tested). [e] The *N*-methyl derivative of this compound was inactive at 600 mg/kg.

III) involved the measurement of the median effective dose (ED_{50}) and the median toxic dose (TD_{50}). The ED_{50} and TD_{50} were determined by administering a range of doses of the test compounds to groups of eight mice until at least three points were established in the range of 10 to 90% seizure protection or minimal neurotoxicity. The data were then plotted and the ED_{50}, TD_{50}, and the 95% confidence interval were evaluated by means of a computer program written by NINCDS.



Scheme I

Results and Discussion

The 2-benzylsuccinimides (**4**) were prepared by treatment of disodiosuccinimide (**3**) in liquid NH_3 with the appropriately substituted benzyl halide.[6] (Scheme I). Phenyl substituents, R_2, were chosen so that each of the three main branches of the Topliss[8] scheme was represented. Physical property data for **4a–f** are summarized in Table IV.

The anticonvulsant activities of **4a–f** were evaluated in the MES and scMet tests. The rotorod test was used to determine the degree of neurotoxicity. Phase I screening data for 2-benzylsuccinimides **4a–f** (Table II) reveal a structure–activity pattern dependent on both the electronic (σ) and lipophilic (π) nature of the phenyl substituent. Thus, **4d** (R_2 = 4-Cl) and **4e** (R_2 = 3,4-Cl_2), having both electron-withdrawing ($+\sigma$) and lipophilic ($+\pi$) substituents, exhibited the greatest and longest lasting activity in the MES and scMet tests. Compound **4f** [R_2 = 4-Si(Me)$_3$] displayed an activity profile similar to that of unsubstituted **4a**, but was longer acting in the MES test. A similar increase in the duration of MES activity has been observed for (4-trimethylsilyl)phenylacetylurea compared with phenylacetylurea.[9] This phenomenon is probably associated with the greater lipophilicity of the trimethylsilylated compounds. Compounds **4b** (R_2 = 4-Me) and **4c** (R_2 = 4-OMe), containing electron-releasing ($-\sigma$) substituents and having lower lipophilicity (π) values,[7b] were the least active. The lack of suitable lipophilicity in **4c** may also account for its low activity compared with the related compound *N*-methyl-2-(4-*n*-butoxybenzyl)succinimide.[4]

2-Benzylsuccinimides **4a**, **4c**, and **4d** exhibited anti-scMet activity similar to that of their corresponding 2-phenylsuccinimide analogues[5] and were somewhat more effective at controlling MES-induced seizures. The same substituent–activity relationship was found in both series, the activity order being 4-Cl > 4-H > 4-OMe. Apparently, a benzyl-for-phenyl substitution in these succinimides does not diminish their anticonvulsant potency as was previously observed following a similar substitution on phenytoin (5,5-diphenylhydantoin).[10] Moreover, while methoxy substituents have been shown to increase the anticonvulsant efficacy of phenytoin,[10] they exert the opposite effect on the activity of

Table III—Phase II Pharmacological Evaluation Data

Compound	ED_{50}[a,b]		TD_{50}[a,c]	PI[d]	
	MES	scMet		MES	scMet
4d	0.5191 (0.4614–0.5714)[e]	0.1825 (0.1135–0.2950)	1.047 (0.8138–1.291)	2.02	5.74
4e	0.4983 (0.3697–0.6343)	0.1757 (0.0437–0.6362)	1.176 (1.024–1.360)	2.36	6.69
1, R_1 = H,R_2 = 4-Cl	0.5756 (0.4792–0.6664)	0.3061 (0.2194–0.4650)	5.149 (4.016–6.226)	8.95	16.82
Ethosuximide	>7.083	0.9237 (0.7863–1.066)	3.122 (2.714–3.438)	—	3.38

[a] ED_{50} and TD_{50} values are mM/kg of test drug delivered ip. [b] Measured at the time of peak effect. [c] Measured at the time of peak neurological deficit. [d] Protective index (TD_{50}/ED_{50}). [e] Numbers in parentheses are 95% confidence intervals.

Table IV—Physical Properties of 2-Benzylsuccinimides 4[a]

Compound	R_2	Yield, %	mp, °C	Recrystallization Solvent	Formula[b]
4a	H	36	95–97.5[c]	EtOH:H_2O	$C_{11}H_{11}NO_2$
4b	4-Me	51	124–126	$CHCl_3$:heptane	$C_{12}H_{13}NO_2$
4c	4-OMe	64	109–111	EtOAc:heptane	$C_{12}H_{10}NO_3$
4d	4-Cl	42	120–122	Toluene:hexane	$C_{11}H_{10}ClNO_2$
4e	3,4-Cl_2	40	118–120	Toluene:heptane	$C_{11}H_9Cl_2NO_2$
4f	4-Si(Me)$_3$	47	138–140	Toluene:hexane	$C_{14}H_{19}SiNO_2$

[a] The IR and ^1H NMR spectra were consistent with assigned structures. [b] All compounds gave satisfactory C, H, and N analyses (+0.4%). [c] Lit.[5] mp 97.5–98 °C.

succinimides. These results, therefore, appear to support the hypothesis that succinimides and hydantoins act via different mechanisms.

On the basis of the encouraging anticonvulsant activity shown in Phase I screening, 2-(4-chlorobenzyl)succinimide (**4d**) and 2-(3,4-dichlorobenzyl)succinimide (**4e**) were advanced to Phase II testing for evaluation of their median effective doses (ED_{50}s) and median toxic doses (TD_{50}s). These pharmacological parameters are displayed in Table III along with similar data for 2-(4-chlorobenzyl)glutarimide (**1**, R_1 = H, R_2 = Cl) and for the clinical drug ethosuximide (2-ethyl-2-methylsuccinimide).[7c] The ED_{50} data indicate that **4d** and **4e** are both about three times more effective against scMet-induced seizures than those induced by MES. Although **4d** and **4e** are more effective than ethosuximide at controlling electrically and chemically induced seizures, they are about three times as neurotoxic. Nevertheless, their protective index (PI) values are more favorable than those of the prototype drug. Compared with **1**, **4d** and **4e** had somewhat better ED_{50}s in the MES and scMet tests, but at the same time were nearly five times as neurotoxic. Consequently, they were not promoted to advanced stages of pharmacological testing.

References and Notes

1. Goehring, R. R.; Greenwood, T. D.; Nwokogu, G. C.; Pisipati, J. S.; Rogers, T. G.; Wolfe, J. F. *J. Med. Chem.* **1990**, *33*, 926–931.
2. (*a*) Coatsworth, J. J.; Paney, J. K. In *Antiepileptic Drugs*; Woodbury, D. M.; Penry, J. K.; Schmidt, R. P., Eds.; Raven: New York, 1972; pp 87–99; (*b*) Ferrendelli, J. A.; Kupferberg, H. J. In *Antiepileptic Drugs: Mechanisms of Action*; Glasser, G. H.; Penry, J. K.; Woodbury, D. M., Eds.; Raven: New York, 1980; pp 587–596.
3. For more recent examples of succinimide anticonvulsants see: (*a*) Campaigne, E.; Yodice, R. *J. Heterocycl. Chem.* **1981**, *18*, 79–83; (*b*) Crider, A. M.; Kolczynski, T. M.; Miskell, D. L. *J. Pharm. Sci.* **1981**, *70*, 192–195; (*c*) Owoyale, J. A.; Lahan, G. D.; Osuide, G.; Edafiogho, I. O. *J. Pharm. Sci.* **1981**, *70*, 963; (*d*) Lange, J.; Rump, S.; Borkowska, G.; Kowalczyk, M.; Lapszewicz, B. M.; Walczyna, K. *Pharmazie* **1984**, *39*, 318–319; (*e*) Kornet, M. J. *J. Pharm. Sci.* **1984**, *73*, 405–406; (*f*) Tarver, M. L.; Nicholson, J. M.; Scott, K. R. *J. Pharm. Sci.* **1985**, *74*, 785–787; (*g*) Borenstein, M. R.; Doukas, P. H. *J. Pharm. Sci.* **1987**, *76*, 300–302.
4. Babiyan, N. A.; Mnatsakanyan, V. A.; Arutyunyan, R. G.; Akopyan, N. E.; Mndzhoyan, O. L. *Izv. Akad. Nauk Arm. SSR, Khim. Nauki* **1964**, *17*, 549–555.
5. (*a*) Miller, C. A.; Long, L. M. *J. Am. Chem. Soc.* **1951**, *73*, 4895–4898; (*b*) Miller, C. A.; Long, L. M. *J. Am. Chem. Soc.* **1953**, *75*, 6256–6258.
6. Bryant, D. R.; Hauser, C. R. *J. Am. Chem. Soc.* **1961**, *83*, 3468–3474.
7. (*a*) Anticonvulsant Screening Project, Antiepileptic Drug Development Program, National Institutes of Health, DHEW Publ (NIH) (U.S.) 1978, NIH 78-1093; (*b*) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409–428; (*c*) Porter, R. J.; Cereghino, J. J.; Gladding, G. D.; Hessie, B. J.; Kupferberg, H. J.; Scoville, B.; White, B. G. *Cleveland Clin. Q.* **1984**, *51*, 293–305.
8. (*a*) Topliss, J. G. *J. Med. Chem.* **1972**, *15*, 1006–1011; (*b*) Topliss, J. G. *J. Med. Chem.* **1977**, *20*, 463–469.
9. Belsky, I.; Gertner, D.; Zilkha, A. *J. Med. Chem.* **1968**, *11*, 451–453.
10. Novelli, A.; DeSantis, A. M. *J. Med. Chem.* **1968**, *11*, 176–178.

Acknowledgments

The authors gratefully acknowledge the generous financial support of this work by the Harvey W. Peters Research Center for Parkinson's Disease and Disorders of the Central Nervous System Foundation and by the National Institute of Neurological and Communicative Disorders and Stroke, Grant Number NS10197. We also thank Gill Gladding and James Stables for providing pharmacological data through the Antiepileptic Drug Development Program, National Institutes of Health.