Potential Anticonvulsants.[1] 1. 5-Benzylhydantoins

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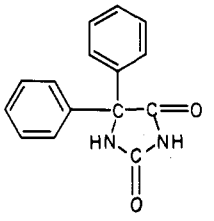
A selected group of alkoxy- and halogen-substitued 5-benzylidino- and 5-benzylhydantoins was prepared and screened for anticonvulsant activity as measured by the ability of the compound to prevent maximal electroshock and metrazol-induced threshold clonic seizures in rats. The structure–activity studies revealed 5-[3-(trifluoromethyl)benzyl]hydantoin (14) to be the most potent member of the series.

Diphenylhydantoin (phenytoin, **23**) was introduced into



phenytoin

medicine over 40 years ago[2] as the result of a well-planned search for a new organic chemical which could suppress electroshock convulsions in animal models corresponding to grand mal (or tonic–clonic) seizures in humans.

Phenytoin is still the drug of choice for the treatment of many seizure disorders and possesses several attractive pharmacological features; however, there are a number of side effects that limit the use of the drug.[3,4] Many derivatives of hydantoin have been prepared in an effort to improve the overall pharmacology of the drug by minimizing some of these less desirable side effects.[5a-c] The studies reported herein focus on the replacement of the phenyl ring of diphenylhydantoin by a potentially more desirable pharmacophore, the benzyl group and its substituted derivatives.

Chemistry. The compounds described were synthesized using known literature methods. Representative examples are included under Experimental Section.

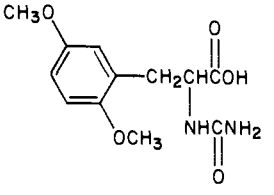
Discussion. A selective study of the anticonvulsant activity of the 5-benzylidinohydantoins and 5-benzylhydantoins was directed toward compounds with limited variations of the basic structure of phenytoin in order to retain the potency associated with this drug. Since a CNS activity was being evaluated, the aryl substituents were chosen so as to increase drug lipophilicity, a characteristic which would enhance passage through the blood–brain barrier.

Initially, alkoxy-substituted derivatives **1–7**, as shown in Table I, were synthesized and screened in rats for both maximal electroshock seizures (MES) and metrazol-induced threshold (clonic) seizures. Compound **1–3**, the 5-(dimethoxybenzyl)-5-methylhydantoin derivatives were inactive in the MES screen even at 50 mg/kg, which is five times the ED_{50} of phenytoin. Even when the 5-methyl substituent on the hydantoin ring was absent, as in compounds **4** and **5**, no improvement in activity was found; this was also true of the corresponding benzylidino precursors (**6** and **7**) and the β-naphthyl analogue (**8**).

By analogy with our earlier work,[6] halogen substituents were introduced into the aromatic nucleus in the 3 position (Table I, compounds **9–15**). It was hoped that this modification would lend itself to an increase in the CNS potency.

None of the 3-chloro or 3-bromo derivatives in this series (**9–12**) showed any significant activity. Only the 3-(trifluoromethyl) substituent of the benzyl series, compound **14**, exhibited marked potency in the MES screen with an ED_{50} = 23 ± 4.5 mg/kg, about half as potent as diphenylhydantoin in the same screen. It had an acceptable acute toxicity level. Unlike diphenylhydantoin, it also showed some effect in the metrazol screen, predictive of effects on absence seizures (petit mal) in humans. Incorporation of the 3-(trifluoromethyl) substituent into compound **23** to give compound **15** resulted in an inactive compound.

Also, the acyclic compounds were investigated for their possible activity as prodrugs similar to those described in the literature.[7] This was done through the alkaline hydrolysis of the parent hydantoins, compounds **5** and **14**, to give the corresponding hydantoic acids, compounds **24** and **25**. These acyclic counterparts were inactive in both



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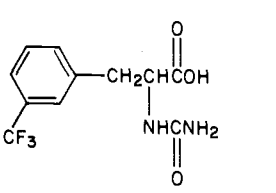

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screens. In the case of compound **25**, the possible prodrug of the active compound **14**, this might possibly be due to a long half-life under in vivo conditions[7] resulting in poor conversion to the cyclized hydantoin.

(1) Portions of this work have been presented; see "Abstracts of Papers", ACS/CSJ Chemical Congress, Honolulu, HI, 1979, American Chemical Society, Washington, D.C., 1979, Abstr MEDI 15.
(2) H. H. Merritt and T. J. Putnam, *J. Am. Med. Assoc.*, 111, 1068 (1938).
(3) D. A. Keith, *J. Oral Surg.*, **36**, 206 (1978).
(4) K. M. Massey, *J. Oral Ther.*, **2**, 380 (1966).
(5) (a) J. E. P. Toman in "The Pharmacological Basis of Therapeutics", 4th ed., L. S. Goodman and A. Gilman, Eds., Macmillian, New York, 1970, p 270; (b) J. A. Vida, M. H. O'Dea, and C. M. Samour, *J. Med. Chem.*, 18, 383 (1975); (c) J. A. Vida, Ed., "Anticonvulsants", Academic Press, New York, 1977, p 176.
(6) N. B. Mehta in "Abstracts of Papers", 175th National Meeting of the American Chemical Society, Anaheim, CA, 1978, American Chemical Society, Washington, D. C., 1978, Abstr MEDI 13.
(7) (a) V. Stella, T. Higuchi, A. Hussain, and J. Truelove in "Prodrugs as Novel Drug Delivery System", T. Higuichi and V. Stella, Eds., American Chemical Society, Washington, D.C., 1975, p 176.

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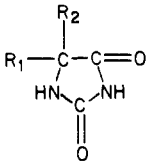
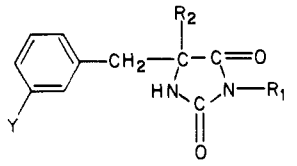
Table I. Pharmacological Activity of the Alkoxy- and Halogen-Substituted Derivatives[a]



no.	max electroshock ED_{50}, mg/kg ip (rats)	metrazol ED_{50}, mg/kg ip (rats)	R_1	R_2	acute toxicity[b] LD_{50}, mg/kg ip (mice)
1[c]	>50		2,4-$(CH_3O)_2C_6H_3CH_2$	CH_3	>600
2[d]	>50	>200	3,4-$(CH_3O)_2C_6H_3CH_2$	CH_3	>500
3[e]	>50		2,5-$(CH_3O)_2C_6H_3CH_2$	CH_3	>800
4[f]	>50	>200	3,4-$(CH_3O)_2C_6H_3CH_2$	H	
5	>50		2,5-$(CH_3O)_2C_6H_3CH_2$	H	
6[g]	>200	>50	3,4-$(CH_3O)_2C_6H_3CH$=		>500
7[h]	>50	>200	2,5-$(CH_3O)_2C_6H_3CH$=		>500
8	>50		β-naphthyl-CH_2	CH_3	
9[i]	~50	>200	3-ClC_6H_4CH=		
10	>50	~150	3-$ClC_6H_4CH_2$	H	
11	>50	>200	3-BrC_6H_4CH=		>500
12[j]	>50	>200	3-$BrC_6H_4CH_2$	H	
13	~50	>200	3-$CF_3C_6H_4CH$=		350
14	23 ± 4.5	~100	3-$CF_3C_6H_4CH_2$	H	350
15	>50	>200	3-$CF_3C_6H_4$	C_6H_5	>100
23	9.6 ± 2.3	*k*	C_6H_5	C_6H_5	100

[a] Compounds were administered ip as a 0.5% suspension in methylcellulose. Compounds 1-4, 6, and 7[13] as well as 9 and 12 have been reported in the literature. [b] Acute Toxicity data courtesy of B. Sezesny and A. Mackars. [c] Melting point 188-189 °C. [d] Melting point 235-237 °C. [e] Melting point 208-210 °C. [f] Melting point 158-161 °C. [g] Melting point 278-280 °C. [h] Melting point 249-251 °C. [i] Melting point 232-234 °C. [j] Melting point 205-207 °C. [k] Potentiation.

Table II. Pharmacological Activity of Compound 14 and Compound 12 Derivatives[a]



no.	max electroshock ED_{50}, mg/kg ip (rats)	metrazol ED_{50}, mg/kg ip (rats)	R_1	Y	R_2	acute toxicity LD_{50}, mg/kg ip (mice)
16	30 ± 6.53	~100	CH_3	Br	H	500
17	>50	>100	CH_3	CF_3	H	350
18	45 ± 12.5	100	CH_2CH_2OH	CF_3	H	
19	>50	>100	CH_2COOEt	CF_3	H	500
20	>50		H	CF_3	CH_3	
21	>50		CH_2CH_2Br	CF_3	H	
22	>50		CH_2CH_2CN	CF_3	H	

[a] Compounds were administered ip as a 0.5% suspension in methylcellulose.

Because of the inherent lack of solubility of the hydantoin derivatives, a considerable number of side effects, such as tissue retention and inflammation at the site of administration, are normally observed; consequently, further synthetic efforts were directed toward preparing N-3 substituted derivatives of compound 14 containing additional lipid-soluble and water-soluble functional groups.

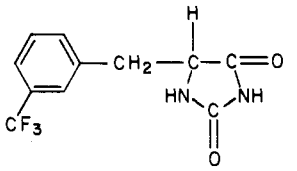
Compound 16 (Table II) with a methyl group on N-3 showed a slight increase in activity over its unmethylated analogue, compound 12, in the MES test. Surprisingly, a loss in activity resulted when compound 14, where the aromatic substitution is trifluoromethyl, was modified in the same way to give compound 17, although it is reported that in vivo metabolism through N-dealkylation converts the 3-methylated product to the unsubstituted hydantoin.[8] Compound 18, the *N*-(hydroxyethyl) derivative, showed only weak anticonvulsant activity in the MES test, although it would be expected to be more hydrophilic. When the substituent R_1 was an ester (19), bromoethyl (21), or cyanoethyl (22), a loss in activity resulted. This behavior might reflect the importance of the N–H linkage in the receptor binding sites. The addition of another substituent at the 5 position (20, $R_2 = CH_3$) resulted in loss of potency.

Pharmacology of 5-[3-(Trifluoromethyl)benzyl]hydantoin (14). A more detailed study of compound 14 was undertaken. Table III gives a brief summary of the comparison of compound 14 with diphenylhydantoin and valproate. Most of the CNS, cardiovascular, and autonomic pharmacology was unremarkable. The duration of action was similar to diphenylhydantoin; however, the acute toxicity by ip route was considerably lower. Unlike diphenylhydantoin it did not develop any kind of tolerance.

Pharmacological Screens. The test compounds were evaluated for their anticonvulsant potency by two standard screens. In both tests the rat was the preferred animal

(8) T. C. Butler, *J. Pharmacol. Exp. Ther.*, 104, 299 (1952).

Table III. Comparison of the Pharmacology of 5-[3-(Trifluoromethyl)benzyl]hydantoin (14), Diphenylhydantoin (23), and Valproate



pharmacological test	route (species)	14	23	valproate[f]
ED_{50}, mg/kg, max electroshock	ip (mice)	70[a]	8.5 ± 2	260
	ip (rat)	23 ± 4.5[a]	9.6 ± 2.3	94.8 ± 5.8
ED_{50}, mg/kg, metrazol	ip (mice)	17.5[a]	50	
	ip (rat)	~100[a]	inactive	>500
ED_{50}, mg/kg, loss of coordination	ip (mice)	65[b]	135	415
ED_{50}, mg/kg, loss of righting reflex	ip (mice)	160[b]	82[c]	
LD_{50}, mg/kg	ip (mice)	350[b]	100[b]	838[d]
	ip (rat)	410[b]	280[b]	1045[d]
	po (rat)		>1000	1530[d]
duration of action, h, MES	ip (rat)	4-6	4-6	~5
developing tolerance	ip (mice)	no	yes	
	po (mice)	no	yes	
pH		5.93[e] (suspn)	11.6 (soln)	6.8 (soln)

[a] Vehicle of administration, 0.5% suspension in methylcellulose. [b] Vehicle of administration, 10% Tween 80 suspension. [c] Vehicle of administration, delayed 24-48 h. [d] See ref 21. [e] Vehicle of administration, 4.2 mg/mL at pH 5.35 in 30% aqueous polyethylene glycol 400 solution. [f] Vehicle of administration, Depakene, 2-propylvalerate dipropylacetate.

model, and saline-treated animals were employed as controls. Compound 23 was used as the reference drug. The acute toxicity data, ip in mice, were determined by the method of Miller and Tainter.[9]

Maximal Electroshock Seizures. Maximal electroshock treatment was administered using a Wahlquist seizure apparatus and corneal electrodes according to the method of Woodbury and Davenport.[10] Sprague–Dawley male rats, weighing 160–300 g, received 150 mA and Blue Spruce (ICR) male mice, weighing 19–22 g, received 50 mA for 0.2 s. Compounds were administered ip or po, at 30 min and 1 h prior to electroshock treatment. Animals were considered protected if the hind-limb extensor component was blocked.

Pentylenetetrazole Convulsions. Pentylenetetrazole convulsions were induced in mice and rats using the method described by Swinyard et al.[11] Animals were pretreated with the test compound ip or po at 30 min and 1 h, respectively. Controls received diluent. All animals received pentylenetetrazole (90 mg/kg ip) and were observed for 15 min. An animal was considered protected if the test compound prevented clonic seizure activity.

Acute Toxicity. The LD_{50} values were calculated using the method of Miller and Tainter[9] based on the results obtained from 6 to 20 animals per dose level.

Experimental Section

Pharmacology. The test compounds were suspended in 0.5% methylcellulose and administered in a volume of 10 mL/kg of body weight, using suspensions at different concentrations. The reference compound, phenytoin sodium salt, was on each occasion freshly prepared in aqueous sodium hydroxide to give a clear solution at pH 11.60.

Peak Time. Peak time of anticonvulsant activity (against MES) was determined in different groups of rats tested at the approximate ED_{84} at 0.5, 1, 2, 3, or >6 h from time of drug administration. Compound 14 had maximal protection against maximal electroshock following intraperitoneal administration of 0.5 h, which is approximately the same as for diphenylhydantoin.

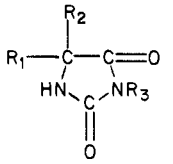
Loss of Righting Reflex. For compound 14, the loss of righting reflex occurred (LRR) at an ED_{50} of 160 mg/kg ip in the mouse and at an ED_{50} of 350 mg/kg ip in the rat. The loss of righting reflex (LRR) for phenytoin in the mouse was 82 mg/kg ip but was delayed 24–48 h following administration.

Neurological Deficit.[20] Neurological deficit was measured in mice using the rotarod test (11 rpm). Those mice which failed to remain on the rotarod for at least 1 min were considered to have loss of coordination. For compound 14, loss of coordination was approximately ED_{50} = 65 mg/kg ip; for phenytoin, it was approximately ED_{50} = 135 mg/kg ip.

Tolerance Study. Compound 14, in doses of 50 and 100 mg/kg, and phenytoin, at 10 mg/kg, were administered ip to mice daily from 5 to 7 days. At various intervals during the study, six

(9) L. C. Miller and M. L. Tainter, *Proc. Soc. Exp. Biol. Med.*, **57**, 261 (1944).
(10) L. A. Woodbury and V. D. Davenport, *Arch. Int. Pharmacodyn. Ther.*, **92**, 97 (1952).
(11) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952). See *DHEW Publ. (NIH) (U.S.)* **NIH 78-1093**, (1978).
(12) H. L. Wheeler and C. Hoffman, *Am. Chem. J.*, **45**, 368 (1911).
(13) Preparation of known compounds in Table I. (a) Compounds 1 and 2: K. Achiwa, S. Terashima, H. Mizuno, N. Takamura, T. Kitagawa, K. Ishikawa, and S. Yamada, *Chem. Pharm. Bull.*, **18**, 61 (1970). (b) Compound 3: F. W. Bollinger and M. Sletzinger, Belgium Patent 614410 (1962); *Chem. Abstr.*, **59**, P1753e. (c) Compound 4: K. Mitsugi, K. Sano, K. Yokoyeki, K. Yamada, I. Noda, K. Teruhiko, C. Eguchi, N. Yasuda, and F. Tamura, U.S. Patent 4016037 (1977). (d) Compound 6: L. Y. Ladna and A. L. Boiko, *Farm Zh.*, **21**, 10 (1966), *Chem. Abstr.*, **65**, 13686d. (e) Compound 7: K. Bharucha, V. Pavilanis, D. Ajdukovic, and H. M. Shrenk, German Offen. 2329745, (1974); *Chem. Abstr.*, **80**, P95948d.
(14) Preparation of compounds in Table I. Compounds 9 and 12: B. A. Ivin, G. V. Rutkovskii, V. A. Kirillova, and E. G. Sochilin, *Reakts. Sposobn. Org. Soedin.*, **6**, 1055 (1969), *Chem. Abstr.*, **73**, 13947W.
(15) H. L. Wheeler and S. H. Clapp, *Am. Chem. J.*, **40**, 458 (1908).
(16) H. R. Henze, W. B. Whitney, and M. A. Eppright, *J. Am. Chem. Soc.*, **62**, 565 (1940).
(17) A. Pinner, *Ber. Dtsch. Chem. Ges.*, **21**, 2320 (1888).
(18) J. W. Shaffer, E. Steinberg, V. Krimsley, and M. B. Winstead, *J. Med. Chem.*, **11**, 462 (1968).
(19) H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942); H. T. Bucherer and H. Fischbeck, *J. Prakt. Chem.*, **140**, 69 (1934).
(20) N. W. Durham and T. S. Mikza, *J. Am. Pharm. Assoc., Sci Ed.*, **46**, 208 (1957).
(21) D. Simon and J. K. Penney, *Epilepsia*, **16**, 549 (1975).

Table IV. Physical Properties of Substituted Hydantoins[a]



no.	R_1	R_2	R_3	procedure	yield, %	mp, °C	solvent[b]	formula
11	3-BrC_6H_4CH=		H	c	37	252-254.5	B	$C_{10}H_7BrN_2O_2$
10	3-$ClC_6H_4CH_2$	H	H	e	58	193-194	B	$C_{10}H_9ClN_2O_2$
13	3-$CF_3C_6H_4CH$=		H	c	63	226.5-228	C	$C_{11}H_7F_3N_2O_2$
14	3-$CF_3C_6H_4CH_2$	H	H	d	85	170.5-172	B	$C_{11}H_9F_3N_2O_2$
16	3-$BrC_6H_4CH_2$	H	CH_3	f	70	147-148	D	$C_{11}H_{11}BrN_2O_2$
17	3-$CF_3C_6H_4CH_2$	H	CH_3	f	87	153-154	D	$C_{12}H_{11}F_3N_2O_2$
20	3-$CF_3C_6H_4CH_2$	CH_3	H	h	20	218-220	A	$C_{12}H_{11}F_3N_2O_2$
5	2,5-$(OCH_3)_2C_6H_3CH_2$	H	H	d	64	171-173	E	$C_{12}H_{14}N_2O_4$
21	3-$CF_3C_6H_4CH_2$	H	CH_2CH_2Br	f	10	114-117	G	$C_{13}H_{12}BrF_3N_2O_2$
18	3-$CF_3C_6H_4CH_2$	H	CH_2CH_2OH	f	22	115-117.5	H	$C_{13}H_{13}F_3N_2O_3$
22	3-$CF_3C_6H_4CH_2$	H	CH_2CH_2CN	g	24	151-152	J	$C_{14}H_{12}F_3N_3O_2$
8	β-naphthyl-CH_2	CH_3	H	h	61	254-255	I	$C_{15}H_{14}N_2O_2$
19	3-$CF_3C_6H_4CH_2$	H	CH_2CO_2Et	f	62	148.5-150	D	$C_{15}H_{15}F_3N_2O_4$
15	3-$CF_3C_6H_4$	C_6H_5	H	h	70	213-214.5	C	$C_{16}H_{11}F_3N_2O_2$

[a] This table is arranged in increasing number of carbon atoms. However, the compound numbers are the same as those in the earlier tables. [b] Solvents: A = methylcellusolve; B = ethanol; C = acetone; D = benzene/hexane; E = methanol/ethyl acetate; F = methylcellusolve/water; G = carbon tetrachloride; H = aqueous ethanol; I = boiling water; J = benzene. [c] Reference 15. [d] See Experimental Section. [e] Reference 16. [f] Reference 17. [g] Reference 18. [h] Reference 19.

mice in each group were tested for protection against maximal electroshock seizures 30 min after dosing. All mice were sacrificed and examined after testing.

Analysis and Spectral Data. Melting points for all compounds were determined in open capillary tubes in a Thomas-Hoover melting point apparatus and are uncorrected. (The melting points for compounds in Table I were not presented in Chemical Abstracts and the corresponding journals were difficult to obtain.) NMR spectra were obtained in $CDCl_3$ or Me_2SO-d_6 with Me_4Si as an internal standard on either a Varian A-60 or Perkin-Elmer 24A spectrometer. Infrared spectra were run as Nujol mulls on a Perkin-Elmer Model 21 spectrophotometer. Mass spectra, where necessary, were recorded on a Varian MAT CH5-DF instrument. Microanalyses were within ±0.3% of the theroretical values.

5-[3-(Trifluoromethyl)benzyl]hydantoin (14). Compound 13 (11.3 g, 0.04 mol) in ethanol (200 mL) was reduced in a Parr hydrogenator using 5% palladium on carbon as a catalyst. The mixture was filtered and concentrated, and the resulting white solid (14) recrystallized from hot ethanol: yield 9.8 g (86%); mp 171-174 °C.

3-(2,5-Dimethoxyphenyl)-2-ureidopropionic Acid (24). It was prepared by the procedure described.[12] Recrystallization from methanol gave a white solid, mp 190.5-191 °C. Anal. ($C_{12}H_{16}N_2O_5$) C, H, N.

Compound **25**, 3-[3-(trifluoromethyl)phenyl]-2-ureidopropionic acid, was prepared in a similar manner and crystallized from boiling ethanol: 50% yield; mp 195-197 °C. Anal. ($C_{11}H_{11}F_3N_2O_3$) C, H, N.

Other compounds were prepared by known procedures as shown in Table IV.

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Synthesis and Antitumor Activity of Simple Vinyl and α-Methylene-γ-butyrolactone Sulfonate Esters and Silyl Enol Ethers[1]

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A number of simple silyl enol ethers and vinyl trifluoromethanesulfonates, a relatively new class of organic compounds capable of undergoing alkylation by a nucleophilic addition–elimination process, were evaluated in the P388 lymphocytic leukemia system. No activity (ILS = 8–22%) was observed in the simple vinyl derivatives. Some activity (ILS = 20–42%) was observed for a series of siloxy and sulfonate (CH_3SO_2 and CF_3SO_3) functionalized α-methylene lactone systems. The enhanced activity of the functionalized systems over the parent methylene lactone is ascribed to a possible *irreversible* alkylation by cellular nucleophiles via a nucleophilic addition–elimination process.

Alkylating agents were one of the first cancer chemoteraputic agents employed and are amongst the most widely and successfully used antitumor agents in clinical use to date.[2] The most recent member of this class of chemoterapeutic agents is the α-methylenebutyrolactone containing sesquiterpenes derived from plant extracts.[3] It

(1) Abstracted in part from the Ph.D. Dissertation of W. L. Treptow, The University of Utah, 1980.

(2) Livingston, R. B.; Carter, S. K. "Single Agents in Cancer Chemotherapy"; Plenum: New York, 1970. Becker, F. F., Ed. "Cancer a Comprehensive Treatise"; Plenum Press: New York, 1977; Vol. 5. Pratt, W. B.; Ruddon, R. W. "The Anticancer Drugs"; Oxford University Press: Oxford, 1979.

0022-2623/81/1824-0468$01.25/0