was crystallized from methylene chloride, ether, and petroleum ether, mp 106-108 °C.

Hypotensive Activity in Rat. The blood pressure of restrained female Sprague-Dawley rats was measured directly from chronic indwelling aortic cannulas exteriorized from the nape of the neck.[6] The rats were restrained in a towel during the period of blood pressure measurement via Statham transducer (P23G) and Grass Model 5 polygraph. Measurements were made before, as well as 4 and 24 h after, the oral administration of each compound suspended in a carboxymethylcellulose vehicle at 10 mL/kg. Blood pressure values of two animals were averaged at each of the three measurement times. An average change of at least 5 mmHg was required posttreatment for statistical significance ($p < 0.05$) to be attained.

Methods for Anesthetized Dogs. The initial cardiovascular evaluation of compound **3a** was carried out in male mongrel dogs which were anesthetized with sodium pentobarbital (30 mg/kg). Polyethylene catheters were inserted into the right femoral artery and vein to monitor arterial blood pressure and to administer drugs, respectively. Bilateral carotid occlusion was accomplished via compression of the exposed carotid arteries with small plastic snares. Blood pressure and heart rate were recorded via a Statham transducer (P23Dc) and a Grass polygraph. Responses to the following tests were recorded: (a) 30-s bilateral carotid occlusion, and intravenous injections of (b) 4 μg/kg acetylcholine, (c) 4 μg/kg norepinephrine, (d) 8 μg/kg histamine, (e) 2 μg/kg isoproterenol, and (f) 0.5 μg/kg angiotensin II. One complete series of tests was carried out before, as well as 30 and 90 min after, the intravenous administration of compound **3a** dissolved in propylene glycol and water (1:1) at 0.5 mL/kg. This volume of vehicle had negligible effects on the recorded parameters and tests in anesthetized control dogs.

In another series of experiments, mongrel dogs of either sex were anesthetized with sodium pentobarbital (30 μg/kg), and the right femoral artery and both femoral veins were cannulated. Blood pressure and heart rate were recorded from the femoral artery catheter via a Statham transducer (P23Dc) and a Grass polygraph. Blood samples were collected and drugs were administered via the femoral venous catheters. Sequential doses of compound **3a**, phentolamine, and minoxidil were given at 90 min intervals as 0.03, 0.3, and 3.0 mg/kg. Prazosin was administered in the same manner in doses of 0.003, 0.03, and 0.3 mg/kg. All drugs were dissolved in propylene glycol and water (1:1) at concentrations allowing volumes of 0.002, 0.02, and 0.2 mL/kg to be administered. Blood samples (1 mL) were analyzed for plasma renin activity by radioimmunoassay utilizing the New England Nuclear angiotensin I (^{125}I) radioimmunoassay kit, which is based on the method of Haber et al.[7]

Methods for Baroreceptor Denervated Cats. Cats of either sex were anesthetized with a mixture of sodium diallylbarbituric acid (60 mg/kg) and urethane (240 mg/kg) administered intraperitoneally. Each animal was positioned in a Kopf stereotaxic apparatus, and a trachea tube was surgically inserted. A femoral artery and vein were cannulated to monitor arterial blood pressure and to administer drugs, respectively. Blood pressure was recorded via a Statham transducer (P23Gc) and a Grass polygraph, while heart rate was recorded continuously with a Grass tachograph triggered by the electrocardiogram. Carotid sinus, aortic depressor, and vagus nerves were exposed and sectioned after reflection of a portion of the trachea and esophagus into the mouth. The sympathetic postganglionic external carotid nerve was isolated distal to its junction with the superior cervical ganglion. Nerve potentials were recorded monophasically under oil with a bipolar platinum electrode after capacity-coupled preamplification (low and high half-amplitude responses at 1 and 500 Hz). Nerve activity was displayed on the polygraph and quantitated using a Grass 7P10B cumulative integrator. Compound **3a** was dissolved in 0.1 M citric acid at a concentration of 1 mg/mL.

Statistical Analysis. Statistical analysis for most experiments was performed using the Student's t test for unpaired comparisons. The values obtained at each time period in the drug-treated groups were compared to the corresponding values in the vehicle group. The 0.05 level of probability was used to indicate statistical significance.

(6) Weeks, J. R.; Jones, J. A. *Proc. Soc. Exp. Biol. Med.* **1960**, *104*, 646.

(7) Haber, E.; Koerner, T.; Page, L.; Kliman, B.; Purnode, A. *J. Clin. Endocrinol.*, **1969**, *29*, 1349.

1-(Naphthylalkyl)-1*H*-imidazole Derivatives, a New Class of Anticonvulsant Agents[1]

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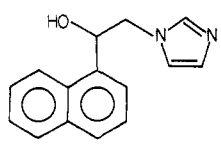
Syntex Research, Palo Alto, California 94304. *Received June 3, 1980*

Potent anticonvulsant activity has been demonstrated for a large number of 1-(naphthylalkyl)-1*H*-imidazoles containing a variety of functional groups in the alkylene bridge. The presence of a small oxygen function in the bridge, in general, confers a high therapeutic index between anticonvulsant and depressant activity. Clinical expectations are discussed for 1-(2-naphthoylmethyl)imidazole hydrochloride (**5**), which is undergoing development for testing in humans.

The new naphthalene compound **42**, prepared in connection with our interest in imidazole-containing antifungal agents, was submitted to pharmacological screening in the mouse based on its structural resemblance to phenethylamines. Following the finding of anticonvulsant activity, and in view of the clearly expressed need[2] for more selective and less toxic anticonvulsant drugs, we initiated a synthetic program based on this lead. A series of analogues of **42** was prepared and evaluated for anticonvulsant activity in the maximal electroshock assay, with the goal of identifying a compound with an enhanced therapeutic index relative to currently available drugs.



42

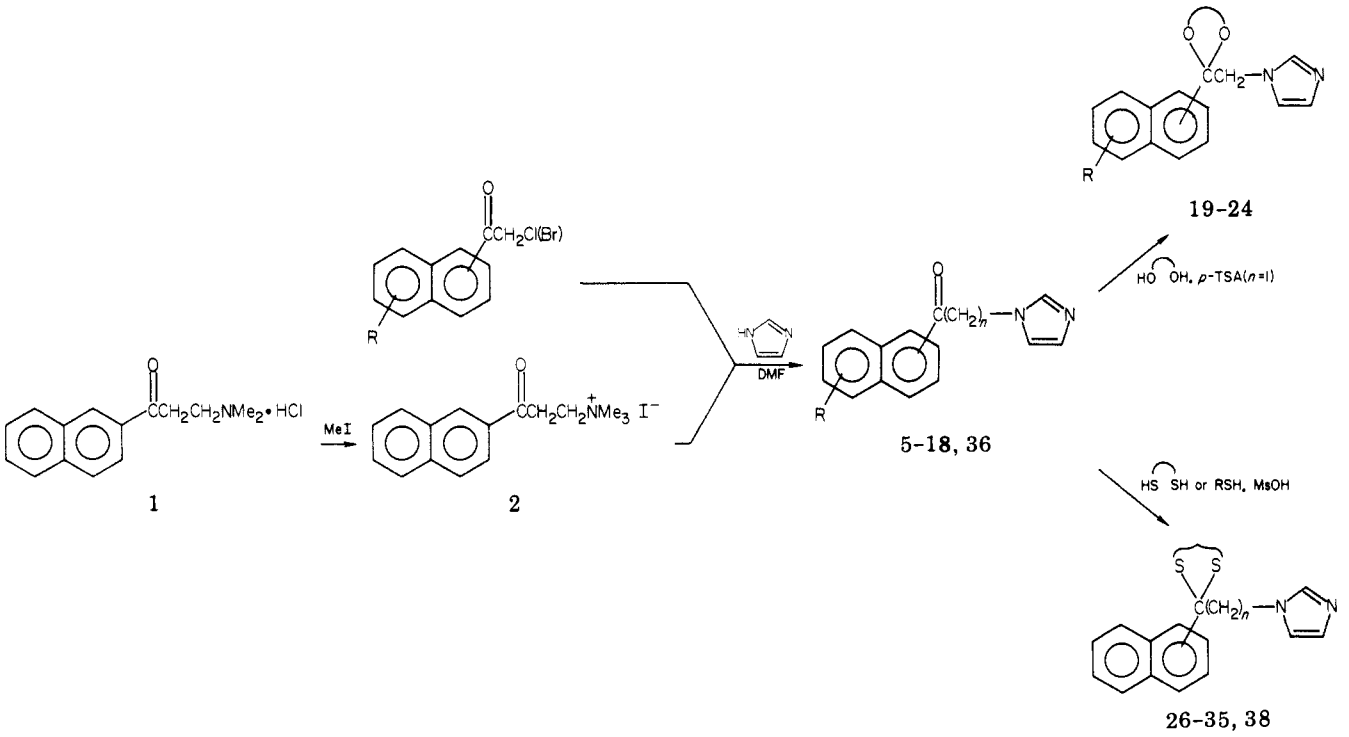
Chemistry. All but four of the title compounds are *N*-(naphthoylalkyl)imidazoles or are synthetically accessible therefrom. The ketones **5-18** were prepared by al-

(1) Contribution no. 557 from the Institute of Organic Chemistry, Syntex Research, Palo Alto, CA 94304.

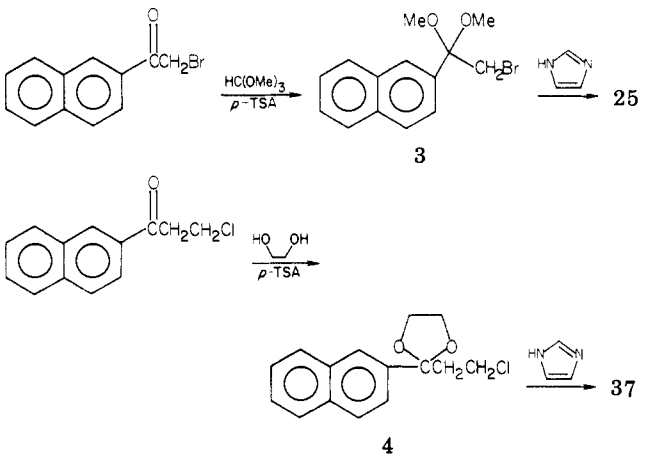
(2) R. L. Krall, J. K. Penry, B. G. White, H. J. Kupferberg, and E. A. Swinyard, *Epilepsia*, **19**, 409-428 (1978). For a discussion of the side effects of anticonvulsant drugs, see M. J. Eadie, *Drugs*, **17**, 213 (1979).

0022-2623/81/1824-0067$01.00/0

Scheme I



Scheme II



kylation of imidazole with the appropriate halomethyl naphthyl ketones (Scheme I). The latter, when not previously described, were obtained by analogy with literature procedures (see Experimental Section). Ketone **36** was most conveniently obtained by quaternization of the Mannich base **1**, followed by reaction with imidazole. The ketals **19–24** were obtained routinely from **5**, **9**, or **13** using excess (2.2 equiv) *p*-TsOH and Dean–Stark conditions; however, preparation of **25** and **37** could not be accomplished directly but was achieved via the haloketals **3** and **4** (Scheme II). Thioketals **26–35** and **38** were obtained from the appropriate ketone using MsOH and excess (di)thiol. Reduction of ketones **5**, **13**, and **36** with $NaBH_4$ gave alcohols **41**, **42**, and **55** (Scheme III), converted routinely to the ethers **43–46** and **56** (NaH/HMPA), esters **50** and **51**, and phenolic ethers **47–49** (Mitsunobu reaction[3]). Thioether **52** was obtained from **41** via the chloride ($SOCl_2$) and MeSNa, and subsequent oxidation (*m*-CPBA) gave **53** and **54**. Compounds **39** and **40** were prepared from the known halides and imidazole (Scheme IV).

Biological Methods. The anticonvulsant activity of compounds **5–56** was determined using the maximal electroshock seizure test[4] (MES) in mice (ip). Immediately prior to electroshock, a traction test[5] was conducted to measure the neurological deficit produced by the compound. In this test, ataxia and sedation are indicated by the inability of the mice to remain on a horizontal wire for 10 s. The dose causing a neurological deficit in 50% of the animals (ND_{50}) is determined and used to calculate the protective index (PI) of the compound (ND_{50} divided by the MES ED_{50}). Compounds having a potential clinically useful profile are distinguished from CNS depressant compounds also active in the MES assay by a large value of the protective index (PI). Oral activity was also determined for the most promising compounds, with further evaluation of selected compounds being made in the rat. LD_{50} values were estimated from behavior studies (ip mouse). (See Experimental Section for detailed methods.)

Results

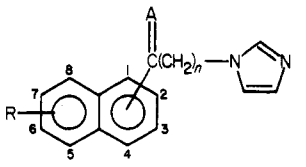
Structure–Activity Relationships. The test results presented in Table III show anticonvulsant activity to be a rather general property of 1-(naphthylalkyl)imidazole derivatives, extending over a remarkable variety of structural types—ketones, cyclic ketals, cyclic and acyclic thioketals, alcohols, ethers, esters, and homologues, but not sulfoxide or sulfone. Attachment at either position of the naphthalene ring is permissible, and although the 2-isomers are generally more active (e.g., **5**, **19**, **43**), this is not necessarily the case (**28**, **42**). However, the marked enhancement of activity in the 2-naphthyl ketone **5** compared with the earlier lead **13** encouraged most further modifications to be made in the 2-naphthyl series. In both series, the most desirable anticonvulsant properties are associated with the presence of a small oxygen-containing

(3) M. S. Manhas, W. H. Hoffman, B. Lal, and A. K. Bose, *J. Chem. Soc., Perkin Trans. 1*, 461 (1975).

(4) E. A. Swinyard, W. C. Brown, and L. S. Goodman, *J. Pharmacol. Exp. Ther.*, **106**, 319 (1952).

(5) R. A. Turner, "Screening Methods in Pharmacology", Academic Press, New York, 1965, p 89.

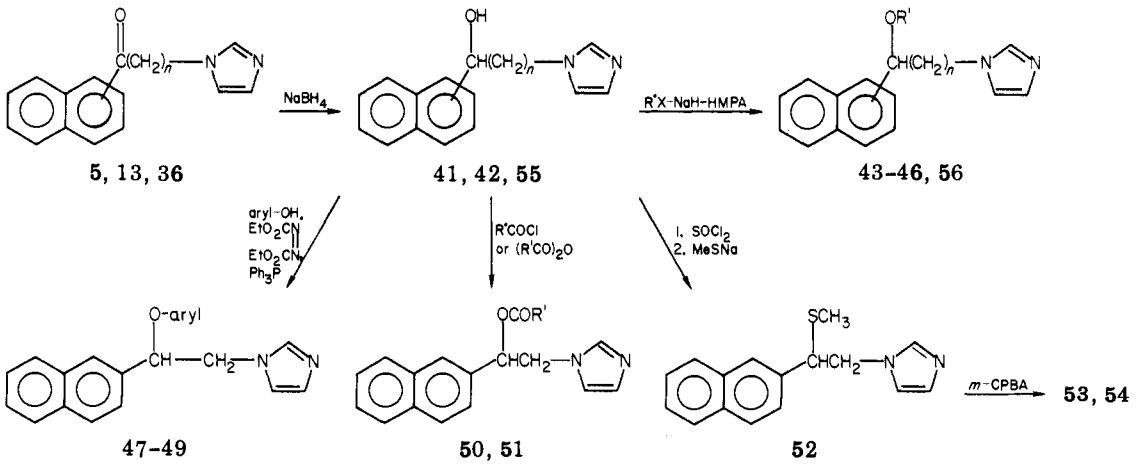
Table I. Naphthoylalkylimidazoles



no.	A	R	naphthyl	n	solvent[a]	mp, °C	formula	anal.[b]
5	O		2	1	B	226-228.5[d]	$C_{15}H_{12}N_2O\cdot HCl$	C, H, N
6	O	6-Cl	2	1	B	277-279	$C_{15}H_{11}ClN_2O\cdot HCl$	C, H, N
7	O	6-Br	2	1	E	283.5-287[d]	$C_{15}H_{11}BrN_2O\cdot HCl$	C, H, N
8	O	6-CH_3	2	1	B	271-272[d]	$C_{16}H_{14}N_2O\cdot HCl$	C, H, N
9	O	6-C_2H_5	2	1	A	263.5-264	$C_{17}H_{16}N_2O\cdot HBr$	C, H, N
10	O	6,7-$(CH_3)_2$	2	1	C	239.5-243	$C_{17}H_{16}N_2O\cdot HCl$	C, H, N
11	O	6-OCH_3	2	1	E	233-237[d]	$C_{16}H_{14}N_2O_2\cdot HCl$	C, H, N
12	O	1-OCH_3	2	1	E	170-172.5	$C_{16}H_{14}N_2O_2\cdot HCl$	C, H, N
13	O		1	1	J	113.5-117	$C_{15}H_{12}N_2O$	C, H, N
14	O	7-CH_3	1	1	D	241.5-244	$C_{16}H_{14}N_2O\cdot HCl$	C, H, N
15	O	7-C_2H_5	1	1	A	187.5-190.5	$C_{17}H_{16}N_2O\cdot HBr$	C, H, N
16	O	4-$CH(CH_3)_2$	1	1	B	199.5-203	$C_{18}H_{18}N_2O\cdot HCl$	C, H, N
17	O	6,7-$(CH_3)_2$	1	1	D	271-274	$C_{17}H_{16}N_2O\cdot HCl$	C, H, N
18	O	6,7-$(OCH_3)_2$	1	1	B	267.5-270	$C_{17}H_{16}N_2O_3\cdot HCl$	C, H, N
19	OCH_2CH_2O		2	1	B	269-270	$C_{17}H_{16}N_2O_2\cdot HCl$	C, H, N
20	$O(CH_2)_3O$		2	1	B	258.5-260[d]	$C_{18}H_{18}N_2O_2\cdot 0.5H_2O\cdot HCl$	C, N; H[e]
21	$OCH(CH_3)(CH_2)_2O$		2	1	B	218.5-220	$C_{19}H_{20}N_2O_2\cdot HCl$	C, H, N
22	$OCH_2C(CH_3)_2CH_2O$		2	1	B	284.5-288	$C_{20}H_{22}N_2O_2\cdot HCl$	C, H, N
23	OCH_2CH_2O	6-C_2H_5	2	1	B	251[c]	$C_{19}H_{20}N_2O_2\cdot HCl$	C, H, N
24	OCH_2CH_2O		1	1	B	256.5-257	$C_{17}H_{16}N_2O_2\cdot HCl$	C, H, N
25	$(OCH_3)_2$		2	1	G	119.5-121.5	$C_{17}H_{18}N_2O_2$	C, H, N
26	SCH_2CH_2S		2	1	F	248.5-253	$C_{17}H_{16}N_2S_2\cdot 0.5H_2O\cdot HCl$	C, H, N
27	$S(CH_2)_3S$		2	1	D	261.5-262.5[d]	$C_{18}H_{18}N_2S_2\cdot HCl$	C, H, N
28	SCH_2CH_2S		1	1	D	229.5-232.5	$C_{17}H_{16}N_2S_2\cdot HCl$	C, H, N
29	$(SCH_3)_2$		2	1	B	209[d]	$C_{17}H_{18}N_2S_2\cdot HCl$	C, H, N
30	$(SC_2H_5)_2$		2	1	H	205-208.5	$C_{19}H_{22}N_2S_2\cdot HCl$	C, H, N
31	$(S\text{-}n\text{-}C_3H_7)_2$		2	1	A	188-189.5	$C_{21}H_{26}N_2S_2\cdot HCl$	C, H, N
32	$(S\text{-}i\text{-}C_3H_7)_2$		2	1	B	232.5-235	$C_{21}H_{26}N_2S_2\cdot HCl$	C, H, N
33	$(S\text{-}i\text{-}C_4H_9)_2$		2	1	E	158.5-161	$C_{23}H_{30}N_2S_2\cdot HCl$	C, H, N
34	$(SC_6H_5)_2$		2	1	D	180-182.5[d]	$C_{27}H_{22}N_2S_2\cdot HCl$	C, H, N
35	$(SCH_2C_6H_5)_2$		2	1	D	181-182	$C_{29}H_{26}N_2S_2\cdot HCl$	H, N; C[f]
36	O		2	2	B	182.5-186	$C_{16}H_{14}N_2O\cdot HCl$	C, H, N
37	OCH_2CH_2O		2	2		155-157	$C_{18}H_{18}N_2O_2$	C, H, N
38	SCH_2CH_2S		2	2	D	157-159	$C_{18}H_{18}N_2S_2\cdot HCl$	C, H, N
39	H_2		2	1	E	126.5-129	$C_{15}H_{14}N_2\cdot HCl$	C, H, N
40	H_2		2	0	B	189.5-193.5	$C_{14}H_{12}N_2\cdot HCl$	C, H, N

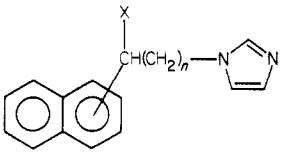
[a] Recrystallization solvents: A, acetone; B, acetone-MeOH; C, CH_2Cl_2-MeOH; D, EtOAc-MeOH; E, EtOAc; F, EtOH; G, toluene; H, EtOH-EtOAc; I, *i*-PrOH; J, benzene. [b] Analytical results within ±0.4 of the theoretical values. [c] Inserted 5 °C before melting point. [d] With decomposition. [e] H: calcd, 5.93; found, 5.41. [f] C: calcd, 69.23; found, 68.60.

Scheme III



substituent in the alkylene bridge, particularly carbonyl (**5, 36**), ethylenedioxy (**19, 24**), methoxy (**43, 45, 56**), acyloxy (**51**), and hydroxy (in **55**), but not acyclic ketal (**25**) or hydroxy (in **41, 42**) at the doses tested. Increasing the size of the substituent decreases both the anticonvulsant activity and the protective index (PI) (**20–22, 44, 47–49**) (PI only in **46**), except for the esters **50** and **51** where this trend is reversed. In this case, the better profile of the larger benzoate ester may be due to more favorable hydrolysis/absorption kinetics.

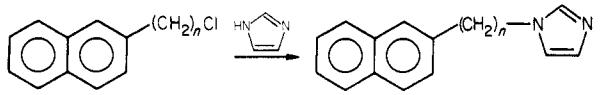
Table II. Substituted Naphthylalkylimidazoles



no.	X	naphthyl	n	solvent[a]	mp, °C	formula	anal.[b]
41	OH	2	1	E	156-160.5	$C_{15}H_{14}N_2O$	C, H, N
42	OH	1	1	E	112.5-115[c]	$C_{15}H_{14}N_2O$	C, H, N
43	OCH_3	2	1	D	171.5-172.5	$C_{16}H_{16}N_2O \cdot HCl$	C, H, N
44	OC_2H_5	2	1	D	109-110.5	$C_{17}H_{18}N_2O \cdot HNO_3$	C, H, N
45	OCH_3	1	1	D	142.5-144	$C_{16}H_{16}N_2O \cdot HNO_3$	C, H, N
46	O-*n*-C_4H_9	1	1	B	109.5-111.5	$C_{19}H_{22}N_2O \cdot HNO_3$	C, H, N
47	OC_6H_5	2	1	B	167-170[c]	$C_{21}H_{18}N_2O \cdot H_2SO_4$	C, H, N
48	*p*-OC_6H_4Cl	2	1	E	162[c]	$C_{21}H_{17}ClN_2O \cdot HCl$	C, H, N
49	*o*-$OC_6H_4CH_3$	2	1	D	223-228[c]	$C_{22}H_{20}N_2O \cdot HCl$	C, H, N
50	$OCOC_2H_5$	2	1	D	160-163	$C_{18}H_{18}N_2O_2 \cdot HCl$	C, H, N
51	$OCOC_6H_5$	2	1	B	219-219.5	$C_{22}H_{18}N_2O_2 \cdot HCl$	C, H, N
52	SCH_3	2	1	B	187-190	$C_{16}H_{16}N_2S \cdot HCl$	C, H, N
53	$S(O)CH_3$	2	1	I	178-180	$C_{16}H_{16}N_2OS \cdot HCl$	C, H, N
54	$S(O)_2CH_3$	2	1	B	199-202[c]	$C_{16}H_{16}N_2O_2S \cdot HCl$	C, H, N
55	OH	2	2	E	166.5-168	$C_{16}H_{16}N_2O \cdot HCl$	C, H, N
56	OCH_3	2	2	D	122-122.5	$C_{17}H_{18}N_2O \cdot H_2SO_4$	C, H, N

[a] See Table I, footnote *a*. [b] See Table I, footnote *b*. [c] With decomposition.

Scheme IV



39, $n = 2$
40, $n = 1$

Sulfur-containing groups are less active than their oxygen counterparts (**26–28, 52**) and, although the smallest member of each series is again the most active (**26, 28, 29**), the compounds are all relatively depressant. The beneficial effect of an oxygen substituent in the bridge is shown by comparison with **39** (and **40**), where anticonvulsant activity is maintained but accompanied by comparable depressant activity. It would appear that an oxygen substituent in the bridge improves the profile by suppressing the depressant component, rather than by enhancing the anticonvulsant activity per se. The presence of a sulfur substituent, on the other hand, confers little benefit. Extension of the bridge to three carbon atoms increases the potency in mice of **36, 38**, and particularly **55** (but not **37** or **56**); however, the protective index is not improved, with the possible exception of **55**. Oral testing (mice) further strengthened the initial promise of compounds **5, 19, 24, 36**, and **43** (Table III).

Aromatic substitution of ketones **5** and **13** in the synthetically most accessible positions (compounds **6–12, 14–18**) gave enhanced activity by the ip route only with certain alkyl substituents (**9, 14–16**). Furthermore, although oral activity was adversely affected by alkyl groups in the 2-naphthyl series (**8, 9**), substitution of the 1-naphthyl ketone **13** with a single alkyl group not only increased activity by the ip route (**14–16**) but gave a compound (**15**) comparable in activity to **5** both ip and po. Unfortunately, similar substitution of the ketal **19** (to **23**) did not afford the same advantage. Testing of selected compounds in rats (Table IV) showed consistently higher activity and selectivity than in mice (ip route), with good oral activity for compounds **5, 19, 24, 36**, and **43**.

Where LD_{50} determinations were made, the more active anticonvulsant compounds appeared to possess clear safety margins of four- to greater than eightfold (in mice). The LD_{50} determined for **5** in the rat (po $LD_{50} > 600$ mg/kg) is particularly noteworthy.

In further screening, compounds **5** and **19** failed to antagonize the clonic seizures induced by pentylenetetrazole. This, together with the profile of activity against toxic extensor seizures elicited by maximal electroshock, implies that the compounds are likely to display a clinical anticonvulsant profile similar to that of phenytoin. They should therefore be useful for generalized tonic–clonic, complex partial, and simple partial seizures in man, but probably not for absence seizures.

Based on the above results and the results of general pharmacological screening, compound **5** (Syntex RS-81943) has been selected for further development as an anticonvulsant agent.[6,7]

Experimental Section

Melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Ultraviolet spectra were determined in methanol with a Cary 14 instrument. Infrared spectra were obtained in KBr with a Perkin-Elmer 237B spectrometer. NMR spectra were obtained with Varian A-60 and HA-100 instruments, and mass spectra were determined with a Varian-MAT CH4 spectrometer. Elemental analyses were performed by the analytical department of Syntex Research, Institute of Organic Chemistry, and are within ±0.4% of calculated values.

1-(Chloroacetyl)-7-ethylnaphthalene and 2-(Chloroacetyl)-6-ethylnaphthalene. Chloroacetyl chloride (15.9 mL, 0.20 mol) was added to anhydrous $AlCl_3$ (26.7 g, 0.20 mol) in 35 mL of $C_6H_5NO_2$ at 0 °C followed by 2-ethylnaphthalene (31.25 g, 0.20 mol) dropwise with stirring over 15 min. After stirring overnight at room temperature, the mixture was poured onto 500 g of ice in 100 mL of concentrated HCl and extracted with EtOAc. The extracts were washed (aqueous K_2CO_3), dried ($MgSO_4$), and evaporated. After distillation of the nitrobenzene, the resulting mixture of isomers was distilled as a yellow oil, bp 177 °C (0.4 mm). Chromatography on silica gel, eluting with toluene, gave 8.75 g (19%) of pure 1-(chloroacetyl)-7-ethylnaphthalene as an

(6) The results of further pharmacological testing on **5** have been presented: M. B. Wallach, L. R. Hedley, K. E. Peterson, and C. Rogers, *Fed. Proc., Fed. Am. Soc. Exp. Biol.*, **39**, 316 (1980).

(7) Following completion of this manuscript, anticonvulsant activity was claimed for related compounds: D. Nardi, A. Tajana, and M. J. Magistretti, German Offen. 2929777 (1980).

oil and 6.3 g (14%) of 2-(chloroacetyl)-6-ethylnaphthalene, recrystallized from hexane with mp 75–76.5 °C. Anal. ($C_{14}H_{13}ClO$) C, H.

The 7-methyl-, 4-isopropyl-, 6,7-dimethyl- and 6,7-dimethoxy-1-(chloroacetyl)naphthalenes were prepared similarly from 2-methyl-, 1-isopropyl-, 2,3-dimethyl-, and 2,3-dimethoxynaphthalene and used directly in the next step. The structures were fully supported by detailed analyses of the NMR spectra.

2-(Bromoacetyl)-6,7-dimethylnaphthalene. 2-Acetyl-6,7-dimethylnaphthalene[8] (1.32 g, 0.00666 mol) and $CuBr_2$ (2.97 g, 0.0132 mol) in 40 mL of $CHCl_3$/EtOAc (1:1) were heated under reflux overnight with vigorous stirring. After the solvent was removed, ether was added, and the solution was filtered and evaporated to yield 1.25 g (68%) of 2-(bromoacetyl)-6,7-dimethylnaphthalene, used directly in the next step.

Similar treatment of 6-chloro-,[9] 6-bromo-,[10] 6-methoxy-, 1-methoxy-,[11] and 6-methyl-2-acetylnaphthalene[12] gave the corresponding 6-chloro-2-(bromoacetyl)-, 6-bromo-2-(bromoacetyl)-,[13] 6-methoxy-2-(bromoacetyl)-, 1-methoxy-2-(bromoacetyl)-,[14] and 6-methyl-2-(bromoacetyl)naphthalene.[15]

1-(2-Naphthoylmethyl)imidazole Hydrochloride (5). To a stirred, ice-cooled slurry of imidazole (35 g, 0.415 mol) in DMF (25 mL) was added bromomethyl 2-naphthyl ketone (24.9 g, 0.1 mol). The mixture was stirred for 2 h at 0 °C and overnight at room temperature. The solution was poured into water, and the resulting sticky solid was filtered off, washed with water, and dissolved in benzene. The resulting benzene solution was dried (azeotroped), filtered, and treated with ethereal HCl. The precipitated salt was crystallized by the addition of EtOAc, and the resulting solid was recrystallized from MeOH–acetone to yield 12.4 g (45%) of **5**, mp 226–228.5 °C dec. Anal. ($C_{15}H_{13}ClN_2O$) C, H, N.

Compounds **6–18** were prepared similarly.

1-[2-(2-Naphthoyl)ethyl]imidazole Hydrochloride (36). 2-Acetonaphthone (34 g, 0.2 mol), paraformaldehyde (13.5 g), Me_2NH·HCl (24.46 g, 0.3 mol), and 0.2 mL of HCl in 100 mL of EtOH were heated under reflux for 24 h. The solvent was removed and the resulting 1·HCl was recrystallized twice from acetone–MeOH to give 31.3 g (59%), mp 173–175 °C (lit.[16] 153–154 °C). Anal. ($C_{15}H_{18}ClNO$) C, H, N. This salt (30.0 g, 0.114 mol) was neutralized with aqueous K_2CO_3 solution, extracted with ether, and dried ($MgSO_4$), and the filtered solution was treated with iodomethane (15 mL, 0.24 mol). The resulting precipitate of [2-(2-naphthoyl)ethyl]trimethylammonium iodide (**2**) was filtered off, washed with acetone, and dried in air to yield 35.5 g (84%), used directly in the next step.

To a stirred, ice-cooled solution of imidazole (4.76 g, 0.07 mol) in 30 mL of dry DMF was added crude **2** (17.66 g, 0.0478 mol). The mixture was stirred overnight at room temperature and at 75 °C for 1 day. The resulting solution was poured into water, and the precipitate was filtered off, washed with water, and dried in air. The product was dissolved in EtOAc and treated with ethereal HCl, and the resulting salt (11.3 g) was filtered off. Recrystallization from MeOH–acetone gave 9.25 g (67%), mp 182.5–186 °C. Anal. ($C_{16}H_{15}ClN_2O$) C, H, N.

1-[2,2-(Ethylenedioxy)-2-(2-naphthyl)ethyl]imidazole Hydrochloride (19). A mixture of 1-(2-naphthoylmethyl)-imidazole hydrochloride (5.45 g, 0.02 mol), ethylene glycol (2.49 g, 0.04 mol), and *p*-TsOH·H_2O (7.6 g, 0.04 mol) in toluene (50 mL) was heated overnight under reflux through a Dean–Stark trap. The trap was then replaced by an addition funnel containing 4Å molecular sieves, and heating continued for a further day. The cooled mixture was treated with 200 mL of EtOAc and poured into excess aqueous K_2CO_3, and the organic phase was separated and dried ($MgSO_4$). The hydrochloride salt was precipitated by the addition of ethereal HCl until precipitation was just complete. Filtration and recrystallization from acetone–MeOH gave 3.9 g (62%) of **19**, mp 269–270 °C. Anal. ($C_{17}H_{17}ClN_2O_2$) C, H, N.

Compounds **20–24** were prepared similarly.

1-[2-(2-Naphthyl)-2,2-dimethoxyethyl]imidazole (25). A solution of bromomethyl 2-naphthyl ketone (2.49 g, 0.01 mol), trimethyl orthoformate (1.7 g, 0.016 mol), and a few crystals of *p*-TsOH (anhydrous) in anhydrous methanol (20 mL) was heated under reflux for 2 h. After the solution was cooled to room temperature, two drops of phenolphthalein solution were added and a solution of MeONa in MeOH was added dropwise until a pink color persisted. After the solvent was removed, the resulting oil was dissolved in ether and decolorized with charcoal, and the ether was removed to give 2.95 g (100%) of **3**.

This ketal (2.21 g, 0.0075 mol) in DMF (5 mL) was added to the salt prepared from sodium hydride (50% dispersion in mineral oil; 0.40 g, 0.0083 mol) and imidazole (0.61 g, 0.009 mol) in DMF (10 mL). The mixture was stirred for 24 h at 110 °C under nitrogen, and the resulting solution was poured into water and extracted with ether. The extracts were washed, dried ($MgSO_4$), and evaporated, and the residue was recrystallized from toluene to give 0.95 g (45%) of **25**, mp 119.5–121.5 °C. Anal. ($C_{17}H_{18}N_2O_2$) C, H, N.

1-[3,3-(Ethylenedioxy)-3-(2-naphthyl)-*n*-propyl]imidazole (33). A solution of 2-chloroethyl 2-naphthyl ketone[17] (1.36 g, 0.0062 mol), ethylene glycol (6.05 g, 0.097 mol), and a crystal of *p*-TsOH·H_2O in 50 mL of toluene was heated for 8 h under reflux through a Dean–Stark trap. After cooling, the mixture was neutralized by pouring into excess aqueous K_2CO_3 and extracted with 200 mL of ether. The organic phase was washed, dried ($MgSO_4$), and evaporated to yield crude **4**. Without further purification the crude ketal (1.36 g, 0.0052 mol) was heated with imidazole (1.77 g, 0.026 mol) in MeCN (2 mL) at 85 °C overnight. After the solvent was removed and water was added, the product was extracted with ether, and the extracts were washed, dried ($MgSO_4$), and evaporated. The residue was chromatographed on silica gel, eluting with 5% MeOH/CH_2Cl_2, to give 0.78 g (43%) of **33**, mp 155–157 °C.

1-[2,2-Bis(*n*-propylthio)-2-(2-naphthyl)ethyl]imidazole Hydrochloride (31). A solution of **5** (2.72 g, 0.01 mol) in 98% methanesulfonic acid (6 mL) was treated at room temperature with *n*-PrSH (4 mL), and the mixture was stirred overnight under N_2. The resulting solution was added to excess aqueous K_2CO_3, the product was extracted with ether, and the extracts were washed and dried ($MgSO_4$). Dropwise addition of ethereal HCl precipitated the hydrochloride, which was recrystallized from acetone–MeOH to give 2.55 g (63%) of **31**, mp 188–189.5 °C. Anal. ($C_{21}H_{27}ClN_2S_2$) C, H, N.

Compounds **26–30**, **32–35**, and **38** were prepared similarly.

1-[2-(2-Naphthyl)ethyl]imidazole Hydrochloride (39). 2-(2-Chloroethyl)naphthalene (4.0 g, 0.021 mol) and imidazole (6.81 g, 0.1 mol) in dry DMF (10 mL) were stirred at 80 °C for 3 days, poured into water (200 mL), and extracted with ether. The extracts were dried ($MgSO_4$) and treated with ethereal HCl, and the oily product was crystallized from EtOAc to give 2.3 g (42%) of **39**, mp 126.5–129 °C. Anal. ($C_{15}H_{15}ClN_2$) C, H, N.

1-(2-Naphthylmethyl)imidazole Hydrochloride (40). 2-(Chloromethyl)naphthalene (8.83 g, 0.05 mol) and imidazole (17.0 g, 0.25 mol) in MeCN (50 mL) were refluxed overnight with stirring, and the solvent was removed. The residue was poured into water and extracted with EtOAc, and the extracts were filtered, washed, and dried ($MgSO_4$). The solution was treated with ethereal HCl, and the resulting hydrochloride salt (9.5 g, 78%) was recrystallized from MeOH–acetone to give **40**, mp 189.5–193.5 °C. Anal. ($C_{14}H_{13}ClN_2$) C, H, N.

1-[2-Hydroxy-2-(2-naphthyl)ethyl]imidazole (41). A solution of **5** (9.4 g, 0.0345 mol) in MeOH (200 mL) at 0–5 °C was treated with excess $NaBH_4$. After the solution was stirred for

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Table III. Anticonvulsant Testing in Mice

	ip			po			
compd	MES ED_{50}, mg/kg	ND_{50}, mg/kg	PI	MES ED_{50}, mg/kg	ND_{50}, mg/kg	PI	LD_{50},[a] mg/kg
5	15 (11-18)[b]	83 (66-92)	5.5	48 (37-60)	>200	>4.2	>100
6	51 (37-68)	>100	>2.0				
7	41 (22-80)						
8	24 (20-28)	>100	>4.3	76 (55-103)	>150	>2.0	>100
9	12 (8-19)	>100	>8.1	84 (60-147)	>100	>1.2	>100
10	25 (13-43)	>100	>4.0	78 (69-90)	>100	>1.3	
11	31 (20-42)	>100	>3.3	>100	>100		>100
12	23 (14-33)	51 (32-90)	2.2				
13	~60						>100
14	22 (18-25)	73 (53-96)	3.3	74 (55-105)	>300	>4.1	
15	13 (12-15)	65 (61-69)	5.0	40 (29-53)	>100	>2.5	
16	28 (23-38)	81 (70-93)	2.9				
17	80 (75-85)	>300	>3.8				
18	79 (62-102)	>100	>1.3				
19	12 (10-14)	31 (21-52)	2.5	18 (13-23)	173 (82-1100)	9.6	>100
20	17 (14-20)	30 (16-49)	1.8	57 (41-77)	>100	>1.7	
21	19 (17-23)	26 (20-35)	1.4	56 (34-89)	>100	>1.8	
22	26 (20-34)	52 (32-89)	2.0	47 (33-62)	>100	>2.1	>100
23	25 (19-33)	>100	>4.0	100 (68-149)	>200	>2.0	
24	19 (16-23)	28 (13-115)	1.5	23 (16-32)	>100	>4.3	
25	>40	>40					
26	26 (16-38)	64 (36-262)	2.4	70 (52-93)	125 (84-325)	1.8	>30
27	65 (55-73)	88 (43 to >1000)	1.4				>100
28	26 (3-32)	57 (39-120)	2.2				
29	32 (23-38)	29 (15-47)	0.9				>100
30	35 (32-39)	78 (57-142)	2.2				>100
31	>100	>100					>100
32	86 (65-95)	>100	>1.2				
33	>100	>100					>100
34	>60	>60					
35	>100	>100					
36	10 (8-13)	60 (41-246)	6.0	20 (15-26)	>100	>5.0	
37	35 (27-41)	>100	>2.9				
38	15 (12-17)	33 (19-51)	2.2				
39	22 (16-26)	31 (22-49)	1.4	47 (39-56)	>100	>2.1	>100
40	25 (19-32)	32 (21-50)	1.3				
41	74 (55-110)						>300
42	34 (31-39)	89 (80-115)	2.6	82 (55-125)	>300	>3.7	>300
43	10 (8-13)	42 (35-49)	4.2	28 (23-40)	110 (79-196)	3.9	
44	11 (8-16)	27 (19-38)	2.5				

45	19 (14–24)	51 (34–82)	2.7					
46	16 (13–19)	27 (25–30)	1.7					
47	15 (9–26)	32 (17–61)	2.1					
48	46 (38–55)	82 (71–93)	1.8					
49	33 (18–48)	70 (57–91)	2.1					
50	23 (18–28)	83 (71–111)	3.6					
51	19 (14–23)	99 (79–125)	5.2					
52	37 (28–44)	76 (53–152)	2.1					
53	>40	>40						
54	>40	>40						
55	13 (8–17)	64 (45–89)	4.9					
56	11 (8–13)	39 (16 to >100)	3.5					
phenytoin	13 (12–15)	>300	>23.1	22 (14–28)	>200	13.6	>300	
phenobarbital	15 (13–18)	30 (17–78)	2.0	19 (16–23)	36 (20–70)	1.9	>100	

[a] Mice, ip administration. [b] 95% confidence limits are included in parentheses.

30 min at 0 °C, the solvent was evaporated and the residue treated with water (200 mL). The product was filtered off, washed with water, and recrystallized from EtOAc to give 7.2 g (88%) of **41**, mp 156–160.5 °C (slight dec). Anal. ($C_{15}H_{14}N_2O$) C, H, N.

Compounds **42** and **55** were prepared similarly.

1-[2-(2-Naphthyl)-2-methoxyethyl]imidazole Hydrochloride (43). To **41** (2.38 g, 0.01 mol) in hexamethylphosphoramide (40 mL) under N_2 was added NaH (56% dispersion in mineral oil; 480 mg, 0.011 mol), and the mixture was stirred for 1 h at room temperature and for 1 h at 50 °C. After the mixture was cooled to about 5 °C, iodomethane (0.74 mL, 0.12 mol) was added dropwise, and the mixture was stirred at 5 to 10 °C for 1 h, at room temperature for 4 h, and at 50 °C for 2 h. The mixture was then poured into water and extracted with ether, and the extracts were washed, dried ($MgSO_4$), and treated with ethereal HCl. Filtration and recrystallization from EtOAc–MeOH gave 1.32 g (46%) of **43**, mp 171.5–172.5 °C. Anal. ($C_{16}H_{17}ClN_2O$) C, H, N.

Compounds **44–46** and **56** were prepared similarly.

1-[2-(2-Naphthyl)-2-(4-chlorophenoxy)ethyl]imidazole Hydrochloride (48). Triphenylphosphine (1.65 g, 0.0063 mol) was added to a stirred mixture of **41** (1.00 g, 0.0042 mol), *p*-chlorophenol (0.81 g, 0.0063 mol), and diethyl azodicarboxylate (0.92, 0.0063 mol) in dry THF (20 mL) at room temperature. The resulting solution was stirred overnight, the solvent was evaporated, and the residual oil was dissolved in ether and treated with ethereal HCl. Crystallization of the precipitated gum from EtOAc gave 1.36 g (84%) of **48**, mp 162 °C dec. Anal. ($C_{21}H_{18}Cl_2N_2O$) C, H, N.

Compounds **47** and **49** were prepared similarly.

1-[2-(Benzoyloxy)-2-(2-naphthyl)ethyl]imidazole Hydrochloride (51). A solution of **41** (1.19 g, 0.005 mol) in pyridine (20 mL) was treated dropwise with stirring with benzoyl chloride (0.72 mL, 0.0062 mol), and the mixture was stirred overnight at room temperature. The resulting solution was poured into water (100 mL) and extracted with EtOAc, and the extracts were washed and dried ($MgSO_4$). After the solvent was evaporated in vacuo to remove residual pyridine, the residue was dissolved in ether and treated with ethereal HCl. The precipitate was recrystallized from acetone–MeOH to give 1.3 g (69%) of **51**, mp 219–219.5 °C. Anal. ($C_{22}H_{19}ClN_2O_2$) C, H, N.

Compound **50** was prepared similarly.

1-[2-(Methylthio)-2-(2-naphthyl)ethyl]imidazole Hydrochloride (52). Thionyl chloride (10 mL) and **41** (2.75 g, 0.0115 mol) were stirred at room temperature for about 20 min and evaporated to dryness, and the residue was treated with EtOAc. Filtration gave 1-[2-(2-naphthyl)-2-chloroethyl]imidazole hydrochloride (3.34 g, 99%) as a white solid. An analytical sample from acetone–MeOH had mp 177.5–178 °C. Anal. ($C_{15}H_{14}Cl_2N_2$) C, H, N.

The crude hydrochloride (3.34 g, 0.0114 mol) was suspended in CH_2Cl_2 and neutralized by shaking with excess aqueous K_2CO_3. The organic layer was separated, dried ($MgSO_4$), and evaporated. The residue in dry THF (10 mL) was added to the salt from MeSH (1.09 g, 0.0226 mol) and NaH (50% dispersion; 0.33 g, 0.0136 mol) in dry THF (30 mL) and stirred overnight at room temperature. After removal of the solvent, water (50 mL) was added, and the product was filtered off, washed with water, and dried. Two recrystallizations from toluene gave the free base (2.35 g). The hydrochloride salt was precipitated from 0.66 g in EtOAc (200 mL) and recrystallized from acetone–MeOH to give 0.56 g (63%) of **52**, mp 187–190 °C.

1-[2-(Methylsulfinyl)-2-(2-naphthyl)ethyl]imidazole Hydrochloride (53). *m*-Chloroperbenzoic acid (85%; 0.6 g, 0.003 mol) in CH_2Cl_2 (10 mL) was added dropwise, with stirring, to the free base of **47** (0.8 g, 0.003 mol) in CH_2Cl_2 (30 mL) at 0 °C. The solution was stirred overnight at room temperature, basified with aqueous K_2CO_3, and extracted with EtOAc. The extracts were dried ($MgSO_4$) and evaporated, and the residue was chromatographed on silica gel, eluting with 20% acetone/CH_2Cl_2, followed by 5% MeOH/CH_2Cl_2. The hydrochloride salt of the pure free base was precipitated from EtOAc using ethereal HCl, and recrystallized from 2-propanol to give 0.40 g (42%) of **53**, mp 178–180 °C. Anal. ($C_{16}H_{17}ClN_2OS$) C, H, N.

1-[2-(Methylsulfonyl)-2-(2-naphthyl)ethyl]imidazole Hydrochloride (54). The free base of **47** (0.8 g, 0.003 mol) was

Table IV. Anticonvulsant Testing in Rats

	ip			po		
compd	MES ED_{50}, mg/kg	ND_{50}, mg/kg	PI	MES ED_{50}, mg/kg	ND_{50}, mg/kg	PI
5	1.7 (0.6-6.6)[a]	>100	>59	26 (13-39)	>100	>3.8
9	5.5 (2.9-19)	>100	>18	>30		
14				52 (31-105)	>100	>1.9
15	3.1 (1.2-6.2)	53 (35-83)	17			
19	4.5 (1.5-6.7)	41 (29-57)	9.1	10 (4.5-19)	>300	>30
24	7.8 (5.3-12)	44 (26-92)	5.6	22 (11-42)	~200	~9
36	5.9 (3.8-8.4)	>60	>10	25 (15-36)	>100	>4.0
39				54 (33-115)	>100	>1.8
40	6.2 (2.2-14)	32 (17-63)	5.2[b]			
42	24 (14-33)	153 (119-211)	6.4	62 (30-125)	>300	>4.8
43	3.8 (2.2-5.3)	46 (31-78)	12	13 (7.3-20)	>100	>7.7
51	14 (8.0-23)	>100	>7.1	53 (34-83)	>100	>1.9
phenytoin	21 (13-32)	>300	>14	85 (51-154)	>300	>3.5

[a] 95% confidence limits are included in parentheses. [b] Stimulation.

treated with *m*-chloroperbenzoic acid (85%; 1.52 g, 0.0075 mol) in methylene chloride (30 mL) for 2 h at room temperature. After workup and extraction as above, the hydrochloride was precipitated and recrystallized from acetone–MeOH to give 0.66 g (65%) of **54**, mp 199-202 °C dec. Anal. ($C_{16}H_{17}ClN_2O_2S$) C, H, N.

Maximal Electroshock Assay. Groups of 8–10 male Hilltop ICR-derived mice weighing 19–30 g or Simonsen Sprague–Dawley derived rats weighing 80–110 g were dosed with compound or aqueous vehicle prior to the administration of a transcorneal electroshock. The mice received 50 mA while rats received 150 mA of a 60-Hz current for 0.2 s. The shock was delivered after testing for a neurological deficit as described below. The pretreatment times were 15 min following ip administration and 30 min following oral administration. The times were fixed since the large number of compounds to be tested did not allow determination of peak activity for each compound.

Immediately prior to the administration of the electroshock, each animal was placed on a 16-gauge, 65-cm long copper wire suspended 40 cm above the table. The ability of a mouse to remain on the wire for 10 s (rat, 8 s) was determined. The quantal data were used to estimate a dose of compound causing a neurological deficit in 50% of the animals (ND_{50}).

The LD_{50} values were estimated from the 5-day survivals of mice subjected to a behavioral screen. Compounds were administered ip in increasing doses to groups of three male Simonsen ICR-derived mice weighing 16–24 g. Deaths were determined on the 5th day.

All quantal data were evaluated by the method of Litchfield and Wilcoxon.[18] The protective index (PI) is the ratio of the deficit-producing dose (ND_{50}) to the anticonvulsant dose (ED_{50}).

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Novel Tetracyclic Spiropiperidines. 1. 3-Aryl-1,3-dihydrospiro[benzo[*c*]thiophene-1,4′-piperidines] as Potential Antidepressants[1a]

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A series of 3-aryl-1,3-dihydrospiro[benzo[*c*]thiophene-1,4′-piperidine] derivatives was synthesized and evaluated pharmacologically for potential psychotropic activity. Potent antidepressant-like activity was noted throughout the series, as assessed by tetrabenazine (TBZ) ptosis prevention in mice and potentiation of 5-hydroxytryptophan (5-HTP) induced behavioral effects in rats. A possible therapeutic advantage of the title compounds appears to be the overall low anticholinergic potential in comparison with the classic tricyclic antidepressants. Several congeners with nuclear halogen substitution also exhibited CNS stimulant properties, as evidenced by their ability to induce a dopamine agonist-like stereotypy and to increase the spontaneous motor activity in mice.

Previous publications from these laboratories[2-5] have documented the pharmacologically diverse responses evoked by structurally varied 3-aryl-1,3-dihydrospiro[isobenzofuran-1(3*H*),4′-piperidines] (I). Marked antide-

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