Synthesis and Anticonvulsant Activity of *N*-(Benzoylalkyl)imidazoles and *N*-(ω-Phenyl-ω-hydroxyalkyl)imidazoles

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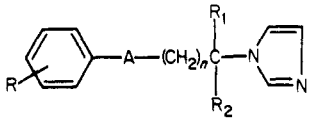
A novel series of *N*-(benzoylalkyl)imidazoles and *N*-(ω-phenyl-ω-hydroxyalkyl)imidazoles was synthesized and evaluated for anticonvulsant activity in mice against maximal electroshock induced seizures. Some of the compounds showed an activity comparable to or better than phenytoin and phenobarbital. The *N*-[β-[4-(β-phenylethyl)phenyl]-β-hydroxyethyl]imidazole (**38**) was selected for further studies; preclinical toxicology and additional efficacy evaluations are in progress. Structure–activity relationships are discussed.

In the course of our research on imidazole derivatives we found an interesting anticonvulsant activity for *N*-(4-phenylphenacyl)imidazole (**13**) and for the corresponding alcohol, namely, *N*-[β-(4-biphenylyl)-β-hydroxyethyl]-imidazole (**33**). This suggested the design and synthesis of related structures of the following general formula in search for more effective anticonvulsant agents:



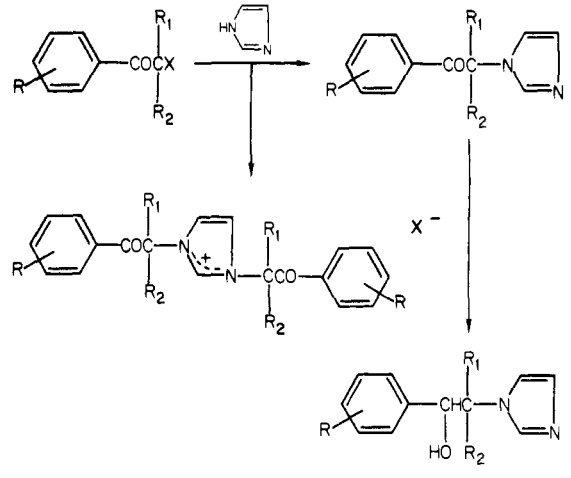
A = CO, CHOH; n = 0, 1

R substituents with different π and σ values were introduced to study the influence of hydrophobic and electronic effects on activity.

The results which evolved during the experimentation indicated that the most interesting compounds had R substituents with higher π values. This observation was in accordance with the statement of Lien[1] on the correlation of the partition coefficient to the anticonvulsant activity. As a result of this, our subsequent research development emphasized the lipophilicity of the substances to be synthesized. We have also considered of interest that the active compounds **13** and **33** contained the biphenyl moiety, whereas the corresponding phenyl derivatives (**42** and **47**) were inactive. This was in accordance with the results of our previous research[2-6] developed on the basis of the "supporting moiety" hypothesis,[7] where we observed that the substitution of a biphenyl, a *sym*-diphenylethane, and a phenyl ether moiety for a phenyl moiety afforded more pharmacologically active compounds. Accordingly, we synthesized new derivatives containing these supporting moieties.

Chemistry. The synthesis of most of the compounds followed the general pathway illustrated in Scheme I. The

Scheme I



N-phenacylimidazoles (Table I) were prepared by reaction of the corresponding aryl α-haloalkyl ketones with imidazole in DMF; the crude product was found (by TLC) to be a two-component mixture, which was separated by column chromatography on silica gel or by the different solubilities of the components. The less soluble components were identified as 1,3-bis(phenacyl)imidazolium halides (see Table II).

The *N*-(β-benzoylalkyl)imidazoles **16**, **17**, and **21** were obtained by reaction of imidazole with the corresponding (β-benzoylalkyl)dimethylamines, which were prepared by a Mannich reaction with the corresponding ketones.

The *N*-(ω-phenyl-ω-hydroxyalkyl)imidazoles (Table III) were prepared by $NaBH_4$ reduction of the corresponding *N*-(benzoylalkyl)imidazoles.

Results

Tables IV and V summarize the data on anticonvulsant activity obtained for the compounds prepared. *N*-Phenacylimidazole (**42**; log P = 1.03) and the corresponding alcohol, namely, *N*-(β-phenyl-β-hydroxyethyl)imidazole (**47**; log P = 0.99), showed no anticonvulsant activity. Also, when hydrophilic substituents (OH, OCH_3, NH_2, $NHCOCH_3$, $NHSO_2CH_3$, NO_2) were introduced into the phenyl moiety (compounds **1–6**, **43**, **22–26**; calcd log P = −0.20 to +1.00), inactive products were obtained. A slight anticonvulsant activity was observed for some monochloro derivatives (calcd log P = 1.69) and for the dichloro derivative **49** (calcd log P = 2.39).

The most active compounds of the series were obtained by introducing in the 4 position of the phenyl moiety of **42** and **47** a cyclohexyl, a phenyl, or a β-phenylethyl group (**10**, **13**, **18**, **30**, **33**, and **38**; calcd log P = 2.95–3.69). The 2-phenyl and 3-phenyl derivatives (**11**, **12**, **31**, and **32**) were also active but more toxic.

(1) E. J. Lien, *J. Med. Chem.*, **13**, 1189 (1970) and references cited therein.
(2) G. Cavallini, E. Massarani, D. Nardi, F. Magrassi, P. Altucci, G. Lorenzutti, and U. Sapio, *J. Med. Pharm. Chem.*, 1, 601 (1959).
(3) G. Cavallini, E. Massarani, D. Nardi, L. Mauri, and F. Magrassi, *Farmaco, Ed. Sci.*, **15**, 503 (1960).
(4) G. Cavallini, E. Massarani, D. Nardi, L. Mauri, and P. Mantegazza, *J. Med. Pharm. Chem.*, **4**, 177 (1961).
(5) G. Cavallini, E. Massarani, D. Nardi, L. Mauri, F. Tenconi, F. Pacchiano, and P. Mantegazza, *J. Med. Chem.*, **6**, 573 (1963).
(6) G. Cavallini, *J. Med. Chem.*, **7**, 255 (1964); G. Cavallini, E. Massarani, D. Nardi, L. Mauri, and F. Tenconi, *Farmaco, Ed. Sci.*, **19**, 964 (1964).
(7) G. Cavallini and E. Massarani, *J. Med. Pharm. Chem.*, 1, 365 (1959).
(8) E. F. Godefroi, J. Heeres, J. Van Cutsem, and P. A. J. Janssen, *J. Med. Chem.*, **12**, 784 (1969).

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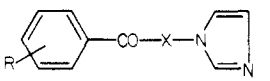
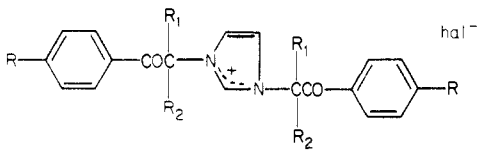
Table I. *N*-(Benzoylalkyl)imidazoles



no.	R	X	method	yield, %	recrystn solvent	mp, °C	formula	anal.
1	3,4-$(HO)_2$	CH_2	A[a]	74	MeOH-H_2O	235-238	$C_{11}H_{10}N_2O_3$	C, H, N
					MeOH-Et_2O	253-254	$C_{11}H_{10}N_2O_3$·HCl	C, H, Cl, N
2	4-HO	CH_2	A[b]	82	EtOH-H_2O	274-278	$C_{11}H_{10}N_2O_2$	C, H, N
					MeOH	254-258	$C_{11}H_{10}N_2O_2$·HCl	C, H, Cl, N
3	4-NO_2	CH_2	A[c]	58	EtOH	164-168 dec	$C_{11}H_9N_3O_3$	C, H, N
					EtOH	238 dec	$C_{11}H_9N_3O_3$·HCl	C, H, Cl, N
4	4-NH_2	CH_2	B	54	EtOH	201-207 dec	$C_{11}H_{11}N_3O$	C, H, N
			C	63	MeOH	277-279	$C_{11}H_{11}N_3O$·HCl	C, H, Cl, N
5	4-CH_3CONH	CH_2	A[b]	82	EtOH	231-233	$C_{13}H_{13}N_3O_2$	C, H, N
					EtOH	264-266	$C_{13}H_{13}N_3O_2$·HCl	C, H, Cl, N
6	4-CH_3SO_2NH	CH_2	D	37	dioxane-H_2O	259-260 dec	$C_{12}H_{13}N_3O_3S$	C, H, N, S
7	4-C_6H_5O	CH_2	A[d]	72	Et_2O	126-127	$C_{17}H_{14}N_2O_2$	C, H, N
					i-PrOH	169-171	$C_{17}H_{14}N_2O_2$·HCl·H_2O	C, H, Cl, N, H_2O
8	4-(*t*-C_4H_9)	CH_2	A[a]	80	ligroin	144-146	$C_{15}H_{18}N_2O$	C, H, N
					EtOH-Et_2O	233-236	$C_{15}H_{18}N_2O$·HCl	C, H, Cl, N
9	4-(*s*-C_4H_9)	CH_2	A[a]	78	cyclohexane	76-79	$C_{15}H_{18}N_2O$	C, H, N
					EtOH-Et_2O	202-206	$C_{15}H_{18}N_2O$·HCl	C, H, Cl, N
10	4-c-C_6H_{11}	CH_2	A[a]	57	benzene	132-133	$C_{17}H_{20}N_2O$	C, H, N
11	2-C_6H_5	CH_2	A[c,e]	46	AcOEt	118-119	$C_{17}H_{14}N_2O$	C, H, N
					EtOH	220-225	$C_{17}H_{14}N_2O$·HCl	C, H, Cl, N
12	3-C_6H_5	CH_2	A[c,d]	40	benzene	128-129	$C_{17}H_{14}N_2O$	C, H, N
					i-PrOH	193-195	$C_{17}H_{14}N_2O$·HCl·0.5H_2O	C, H, Cl, N, H_2O
13	4-C_6H_5	CH_2	A[f]	70	95% EtOH	195-198	$C_{17}H_{14}N_2O$	C, H, N
14	4-C_6H_5	$CHCH_3$	A	56	AcOEt	119-121	$C_{18}H_{16}N_2O$	C, H, N
					i-PrOH	224-227	$C_{18}H_{16}N_2O$·HCl	C, H, Cl, N
15	4-C_6H_5	CH_3CCH_3	A[g]	72	*i*-PrOH	167-168	$C_{19}H_{18}N_2O$	C, H, N
					EtOH	229-232	$C_{19}H_{18}N_2O$·HCl	C, H, Cl, N
16	4-C_6H_5	CH_2CH_2	E	80	EtOH-H_2O	149-151	$C_{18}H_{16}N_2O$	C, H, N
					EtOH	226-229	$C_{18}H_{16}N_2O$·HCl	C, H, Cl, N
17	4-C_6H_5	$CH(CH_3)CH_2$	E	80	benzene	160	$C_{19}H_{18}N_2O$	C, H, N
18	4-$C_6H_5CH_2CH_2$	CH_2	A[a]	64	AcOEt	134-136	$C_{19}H_{18}N_2O$	C, H, N
19	4-$C_6H_5CH_2CH_2$	$CHCH_3$	A[a,h]	54	*i*-PrOH	190-194	$C_{20}H_{20}N_2O$·HCl	C, H, Cl, N
20	4-$C_6H_5CH_2CH_2$	CH_3CCH_3	A[g,h]	33	ligroin	91-92	$C_{21}H_{22}N_2O$	C, H, N
					i-PrOH	191	$C_{21}H_{22}N_2O$·HCl	C, H, Cl, N
21	4-$C_6H_5CH_2CH_2$	CH_2CH_2	E	59	70% EtOH	104-105	$C_{20}H_{20}N_2O$	C, H, N

[a] The reaction was carried out for 24 h. [b] The reaction was carried out for 48 h. [c] At the end of the reaction, the mixture was poured into H_2O-HCl; the unchanged aryl halogenoalkyl ketone was separated by filtration or extraction with Et_2O, and the base was precipitated with NaOH. [d] The reaction was carried out at 20-25 °C. [e] The 2'-phenyl-2-bromoacetophenone was prepared by bromination in $CHCl_3$ at 15-20 °C of 2'-phenylacetophenone; the solution was washed with $NaHCO_3$ and H_2O, the solvent was evaporated, and the crude product was used; the reaction was carried out for 6 h. [f] The reaction was carried out for 12 h. [g] The reaction was carried out at 60 °C for 6 h. [h] The corresponding aryl halogenoalkyl ketone was prepared from *sym*-diphenylethane by Friedel-Crafts reaction with the adequate α-bromoacyl bromide and $AlCl_3$ in $CHCl_3$ at 20-25 °C for 1 h; the crude product was used.

Table II. 1,3-Bis(phenacyl)imidazolium Halides



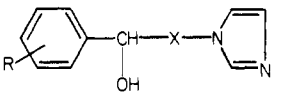
R	R_1	R_2	hal	recrystn solvent	mp, °C	formula	anal.
NO_2	H	H	Br	*i*-PrOH-H_2O	215	$C_{19}H_{15}BrN_4O_6$	C, H, Br, N
t-C_4H_9	H	H	Cl	95% EtOH	257-258	$C_{27}H_{33}ClN_2O_2$	C, H, Cl, N
s-C_4H_9	H	H	Cl	EtOH-Et_2O	230-235	$C_{27}H_{33}ClN_2O_2$	C, H, Cl, N
c-C_6H_{11}	H	H	Cl	EtOH-H_2O	258-261	$C_{31}H_{37}ClN_2O_2$·0.5H_2O	C, H, Cl, N
C_6H_5	H	H	Cl	95% EtOH	250-260	$C_{31}H_{25}ClN_2O_2$	C, H, Cl, N
C_6H_5	CH_3	H	Br	EtOH	224-226	$C_{33}H_{29}BrN_2O_2$	C, H, Br, N
C_6H_5	CH_3	CH_3	Br	EtOH	240-241	$C_{35}H_{33}BrN_2O_2$	C, H, Br, N

Branching or lengthening of the aliphatic chain between imidazole and aryl moieties showed no important effects on the anticonvulsant properties of 4-biphenyl and 4-*sym*-diphenylethane derivatives.

We can observe that the anticonvulsant activity of this series of compounds increases as the lipophilicity increases. However, the activity cannot be related to the log *P* value alone. In fact, the compounds bearing a phenyl ether (**7** and **27**) or a phenyl sulfide[9] moiety, which possesses a partition coefficient comparable to that of the more active compounds of our series, showed only a slight anticon-

(9) R. Cappelletti, A. Tajana, A. Subissi, and D. Nardi, *Boll. Chim. Farm.*, in press.

Table III. N-(ω-Phenyl-ω-hydroxyalkyl)imidazoles



no.	R	X	yield,[a] %	recrystn solvent	mp, °C	formula	anal.
22	3,4-(HO)$_2$	CH_2	40	MeOH	264-267	$C_{11}H_{12}N_2O_3$·HCl	C, H, Cl, N
23	4-HO	CH_2	63[b]	*i*-PrOH	184-185	$C_{11}H_{12}N_2O_2$	C, H, N
				EtOH	184	$C_{11}H_{12}N_2O_2$·HCl	C, H, Cl, N
24	4-CH_3O	CH_2	70	EtOH	196	$C_{12}H_{14}N_2O_2$·HCl	C, H, Cl, N
25	4-NO_2	CH_2	65	EtOH	188-189	$C_{11}H_{11}N_3O_3$	C, H, N
				EtOH	225-229 dec	$C_{11}H_{11}N_3O_3$·HCl	C, H, Cl, N
26	4-NH_2	CH_2	56[c]	MeOH	175-178	$C_{11}H_{13}N_3O$·HCl	C, H, Cl, N
27	4-C_6H_5O	CH_2	78[d]	EtOH	160-162	$C_{17}H_{16}N_2O_2$	C, H, N
				EtOH-Et_2O	175-177	$C_{17}H_{16}N_2O_2$·HCl	C, H, Cl, N
28	4-(*t*-C_4H_9)	CH_2	83	EtOH-H_2O	113-115	$C_{15}H_{20}N_2O$	C, H, N
				EtOH-Et_2O	184-186	$C_{15}H_{20}N_2O$·HCl	C, H, Cl, N
29	4-(s-C_4H_9)	CH_2	78	EtOH-H_2O	124	$C_{15}H_{20}N_2O$	C, H, N
				EtOH-Et_2O	137	$C_{15}H_{20}N_2O$·HCl	C, H, Cl, N
30	4-(c-C_6H_{11})	CH_2	54	EtOH	202-203	$C_{17}H_{22}N_2O$	C, H, N
				EtOH	180-183	$C_{17}H_{22}N_2O$·HCl	C, H, Cl, N
31	2-C_6H_5	CH_2	70	EtOH-Et_2O	227-230	$C_{17}H_{16}N_2O$·HCl	C, H, Cl, N
32	3-C_6H_5	CH_2	57	*i*-PrOH	144-145	$C_{17}H_{16}N_2O$·HCl	C, H, Cl, N
33	4-C_6H_5	CH_2	82	EtOH	183-184	$C_{17}H_{16}N_2O$	C, H, N
				EtOH	235-236	$C_{17}H_{16}N_2O$·HCl	C, H, Cl, N
34	4-C_6H_5	$CHCH_3$	80	90% EtOH	190-192	$C_{18}H_{18}N_2O$	C, H, N
				EtOH	238-242	$C_{18}H_{18}N_2O$·HCl	C, H, Cl, N
35	4-C_6H_5	CH_3CCH_3	89[e]	EtOH	212	$C_{19}H_{20}N_2O$	C, H, N
				i-PrOH	245-246	$C_{19}H_{20}N_2O$·HCl	C, H, Cl, N
36	4-C_6H_5	CH_2CH_2	83	*i*-PrOH	144-145	$C_{18}H_{18}N_2O$	C, H, N
				i-PrOH	188-189	$C_{18}H_{18}N_2O$·HCl	C, H, Cl, N
37	4-C_6H_5	$CH(CH_3)CH_2$	66	95% EtOH	153-156	$C_{19}H_{20}N_2O$	C, H, N
				EtOH	179-182	$C_{19}H_{20}N_2O$·HCl	C, H, Cl, N
38	4-$C_6H_5CH_2CH_2$	CH_2	79	EtOH	165-166	$C_{19}H_{20}N_2O$	C, H, N
				EtOH	194-196	$C_{19}H_{20}N_2O$·HCl	C, H, Cl, N
39	4-$C_6H_5CH_2CH_2$	$CHCH_3$	58	70% EtOH	116-117	$C_{20}H_{22}N_2O$	C, H, N
				i-PrOH	150-163	$C_{20}H_{22}N_2O$·HCl	C, H, Cl, N
40	4-$C_6H_5CH_2CH_2$	CH_3CCH_3	73	AcOEt	125-127	$C_{21}H_{24}N_2O$	C, H, N
				i-PrOH-Et_2O	183-184	$C_{21}H_{24}N_2O$·HCl	C, H, Cl, N
41	4-$C_6H_5CH_2CH_2$	CH_2CH_2	76	EtOH	148-149	$C_{20}H_{22}N_2O$	C, H, N
				i-PrOH	160-162	$C_{20}H_{22}N_2O$·HCl	C, H, Cl, N

[a] All compounds, except 26, were prepared according to method F. [b] The reaction was carried out with 0.02 mol of $NaBH_4$ and 0.01 mol of NaOH. [c] See method G. [d] In the reaction, 0.012 mol of $NaBH_4$ was used. [e] In the reaction, 40 mL of MeOH was used.

vulsant activity, suggesting the importance of other parameters. It is remarkable to note that some compounds showed an anticonvulsant activity comparable to or better than phenytoin and phenobarbital.

N-[β-[4-(β-Phenylethyl)phenyl]-β-hydroxyethyl]-imidazole (**38**) was selected for further studies. Preclinical toxicology and additional efficacy evaluations are in progress.

Experimental Section

Melting points were determined using a Büchi melting point apparatus and are uncorrected. Analytical results for indicated elements and, where appropriate, H_2O are within ±0.4% of the theoretical values. ^1H NMR 60-MHz spectra, recorded with a Perkin-Elmer R 24A instrument, and IR spectra, determined on a Perkin-Elmer 257 spectrophotometer, support the structural assignments. Purity of all compounds was checked by TLC with Merck Kieselgel G.F. 254 plates. Column chromatography was accomplished using Merck Kieselgel 60.

4′-Cyclohexyl-2-chloroacetophenone. A mixture of cyclohexylbenzene (16 g, 0.1 mol) and chloroacetyl chloride (11.29 g, 0.1 mol) was added dropwise at 10–15 °C over 1 h to a stirred mixture of $AlCl_3$ (13.3 g, 0.1 mol) and 60 mL of CS_2. Stirring was continued for 6 h at 10–15 °C, and then the reaction mixture was poured into ice–HCl and extracted with CH_2Cl_2. The extract was washed with H_2O and dried (anhydrous Na_2SO_4). After the solvent was evaporated, the residue was distilled: bp 140–150 °C (0.6 mmHg); yield 18 g (75%). A sample was crystallized from EtOH–H_2O, mp 47–49 °C. Anal. ($C_{14}H_{17}ClO$) C, H, Cl.

General Procedure for the Preparation of *N*-Phenacylimidazoles. Method A. A mixture of the appropriate phenacyl halide (0.01 mol), imidazole (0.05 mol), and 3 mL of DMF was stirred at 5–10 °C for 3 h. Then it was poured into H_2O, and the precipitate was collected and washed with H_2O. The crude product was a mixture of the *N*-phenacylimidazole and the corresponding 1,3-bis(phenacyl)imidazolium halide which were separated by their different solubility in apolar or slightly polar solvents, such as ligroin, benzene, or toluene, which gave solutions containing only the *N*-phenacylimidazole. Sometimes the components of the mixture were separated by column chromatography, eluting with AcOEt or Me_2CO; the first fractions gave the more soluble *N*-phenacylimidazoles, whereas the 1,3-bis(phenacyl)-imidazolium halides were eluted later or not at all. Yields, melting points, solvents of crystallization, and analyzed elements are reported in Table I for the *N*-phenacylimidazoles and in Table II for the 1,3-bis(phenacyl)imidazolium halides.

***N*-(4-Aminophenacyl)imidazole (4). Method B.** A solution of *N*-(4-nitrophenacyl)imidazole hydrochloride (**3**; 2.67 g, 0.01 mol) in 40 mL of 50% MeOH was reduced with H_2 in the presence of 5% Pd/C catalyst (0.2 g) to completion (0.06 mol of H_2 uptake). After the solution filtered, the solvent was evaporated and the residue was crystallized.

Method C. A solution of *N*-(4-acetamidophenacyl)imidazole (**5**; 2.43 g, 0.01 mol) in 5 mL of 2 N HCl was refluxed for 30 min. After the solution cooled, the base was precipitated by adding NaOH, collected, and crystallized (see Table I).

***N*-[4-(Methanesulfonamido)phenacyl]imidazole (6). Method D.** A solution of *N*-(4-aminophenacyl)imidazole (**4**; 2.01 g, 0.01 mol) in 10 mL of HMPA was added to $MeSO_2Cl$ (1.14 g, 0.01 mol) in 1.6 mL of pyridine, and the mixture was heated at 80 °C for 6 h. After the mixture cooled, it was poured into H_2O.

Table IV. Anticonvulsant Activity in Mice of *N*-(Benzoylalkyl)imidazoles[a]

compd	LD_{50}, mg/kg ip	LD_{50}, mg/kg po	electroshock ED_{50}, mg/kg ip	electroshock ED_{50}, mg/kg po
42[b]	360		>72	
1	1000		>200	>200
2	750		>150	>150
43[c]	270		>54	
3	360		>72	>72
4	360		>72	>72
5	1000		>200	>200
6	>3000	>3000	>300	>300
44[d]	360		51[e]	44[e]
45[f]	240		>48	>48
46[g]	420		>84	>84
7	100		>20	>20
8	100		>20	>20
9	115		>23	>23
10	>3000	2100	62.2 (37.5-103.2)[h]	89.9 (76-106.3)
11	115	360	13.5[e]	17.1 (15.9-18.3)
12	210	750	11.2 (9.2-13.7)	21[e]
13	1550	2400	61.3 (44.2-85)	78.3 (48.7-126)
14	87.5		13.4[e]	>18
15	>3000	1870	38 (29.6-48.7)	42.9 (30-61.4)
16	360	1150	35.1 (28.9-42.5)	40.5[e]
17	130		19.5[e]	>26
18	300		12.7 (10.6-15.1)	36.9 (29.4-46.1)
19	115		>23	>23
20	180		29.5[e]	>36
21	>3000	2100	28.6 (23-35.6)	112.5 (86.5-146)
phenytoin	194	284	8.5 (7.6-9.5)	9.7 (8.7-10.8)
phenobarbital	235	237	22.5 (19.4-26)	17.6 (14.9-20.8)

[a] All compounds were tested as hydrochloride or nitrate salts, except compounds 6, **10**, 13, **17**, **18**, and 21, which were tested as bases. [b] *N*-Phenacylimidazole.[8] [c] *N*-(4-Methoxyphenacyl)imidazole.[8] [d] *N*-(2-Chlorophenacyl)imidazole.[8] [e] Graphycally calculated. [f] *N*-(4-Chlorophenacyl)imidazole.[8] [g] *N*-(2,4-Dichlorophenacyl)imidazole.[8] [h] 95% confidence limits, in parentheses, are calculated according to the method of ref 15.

Table V. Anticonvulsant Activity in Mice of *N*-(ω-Phenyl-ω-hydroxyalkyl)imidazoles[a]

compd	LD_{50}, mg/kg ip	LD_{50}, mg/kg po	electroshock ED_{50}, mg/kg ip	electroshock ED_{50}, mg/kg po
47[b]	210		>42	
22	1150		>230	>230
23	1000		>200	>200
24	360		>72	
25	490		98[c]	98[c]
26	875		>175	>175
48[d]	270		31[c]	>54
49[e]	300		39.7[c]	39.7[c]
27	360		31.1[c]	>48
28	210		42[c]	>42
29	210		28.5[c]	31.2[c]
30	490	2700	53 (41.4-67.4)[f]	59.6 (51.9-68.3)
31	155	300	18.8[c]	24.5[c]
32	180		15.8 (13.1-19.1)	25[c]
33	1150	>3000	45 (31.9-63.4)	31 (21.4-44.8)
34	655	570	19.6 (16.1-23.7)	24.7 (21.7-28.1)
35	420	2400	23.8 (19.3-29.3)	25.1 (21.1-29.8)
36	360		44[c]	53.5[c]
37	210		25.7[c]	32.3[c]
38	270	434	5.3 (4.4-6.3)	10.2 (7.7-13.5)
39	180		15[c]	36[c]
40	240		22.4[c]	>48
41	420	560	21[c]	24.7 (19.4-31.4)
phenytoin	194	284	8.5 (7.6-9.5)	9.7 (8.7-10.8)
phenobarbital	235	237	22.5 (19.4-26)	17.6 (14.9-20.8)

[a] All compounds were tested as hydrochloride salts, except compounds **48** and **49**, which were tested as bases. [b] *N*-(β-Phenyl-β-hydroxyethyl)imidazole.[8] [c] Graphically calculated. [d] *N*-[β-(4-Chlorophenyl)-β-hydroxyethyl]imidazole.[8] [e] *N*-[β-(2,4-Dichlorophenyl)-β-hydroxyethyl]imidazole.[8] [f] 95% confidence limits, in parentheses, are calculated according to the method of ref 15.

The separated precipitate was collected and crystallized (see Table I).

4′-Phenyl-2-methyl-3-(dimethylamino)propiophenone. To a solution of dimethylamine hydrochloride (16.3 g, 0.2 mol) in 15 mL of 40% aqueous CH_2O was added 20 mL of Ac_2O, and the mixture was stirred at 20–25 °C for 30 min and then warmed to 120 °C. After 30 min, a boiling solution of 4′-phenylpropiophenone (42 g, 0.2 mol) in 30 mL of Ac_2O was added, and the mixture was refluxed for 15 min. The solvent was evaporated under reduced pressure, and the residue was dissolved in H_2O and extracted with Et_2O to remove the unchanged 4′-phenylpropiophenone. The aqueous layer was alkalinized with Na_2CO_3, and the separated

base was collected and washed with H_2O: yield 46.5 g (87%); mp 59 °C. Anal. ($C_{18}H_{21}NO$) C, H, N. The hydrochloride was prepared by conventional procedure and was crystallized from *i*-PrOH, mp 187 °C. Anal. ($C_{18}H_{21}NO$·HCl) C, H, Cl, N.

4′-(β-Phenylethyl)-3-(dimethylamino)propiophenone was prepared according to the above procedure from 4′-(β-phenylethyl)acetophenone. The hydrochloride was prepared by conventional procedure and crystallized from *i*-PrOH: yield 70%; mp 144–145 °C. Anal. ($C_{19}H_{23}NO$·HCl) C, H, Cl, N.

***N*-[β-(4-Phenylbenzoyl)ethyl]imidazole (16). Method E.** A stirred mixture of 4′-phenyl-3-(dimethylamino)propiophenone hydrochloride (2.9 g, 0.01 mol), imidazole (0.68 g, 0.01 mol), and 15 mL of 50% EtOH was refluxed for 3 h. After the mixture cooled, the separated crystals were collected and recrystallized (see Table I).

General Procedure for the Preparation of *N*-(ω-Phenyl-ω-hydroxyalkyl)imidazoles. Method F. A mixture of the appropriate *N*-(benzoylalkyl)imidazole (0.01 mol), $NaBH_4$ (0.38 g, 0.01 mol), and 20 mL of MeOH was refluxed for 2 h. After solvent evaporation, 20 mL of H_2O was added to the residue. The mixture was neutralized with dilute HCl and than refluxed for 30 min. After the mixture cooled, the solution was alkalinized with NaOH, and the precipitate was collected and crystallized. Yields, melting points, solvents of crystallization, and analytical data are reported in Table III.

***N*-[β-(4-Aminophenyl)-β-hydroxyethyl]imidazole (26). Method G.** A solution of *N*-[β-(4-nitrophenyl)-β-hydroxyethyl]imidazole hydrochloride (**25**; 2.69 g, 0.01 mol) in 40 mL of 50% MeOH was reduced with H_2 in the presence of 5% Pd/C catalyst (0.2 g) in a Parr apparatus with an initial pressure of 60 psi. After the solution was filtered, the solvent was evaporated and the residue was crystallized (see Table III).

Determination of Partition Coefficients. Partition coefficients of *N*-phenacylimidazole (**42**) and *N*-(β-phenyl-β-hydroxyethyl)imidazole (**47**) were experimentally measured by a modified Hansch procedure, employing a 1-octanol/phosphate buffer (0.2 M, pH 7.4, ionic strength adjusted to 0.5 with KCl) system. Partitioning was carried out at room temperature (20 ± 5 °C) with gentle shaking for 6 h. After centrifugation (15 min at 2000 rpm), the octanol phase was analyzed by gas chromatography (Hewlett Packard 5830A instrument). The amount of solute found was then subtracted from the total sample to obtain the amount in the second phase. Three repetitions were made to ensure an unforeseen loss.

The observed log P_{app} values were corrected by ionization according to the formula[10] $\log P = \log P_{app} - \log (1/1 + 10^{pK_a'-pH})$, obtaining log *P* values of 1.03 for **42** and 0.99 for **47**. The calculated log *P* values reported in the text were obtained by adding the π values taken from the compilation of Hansch et al.[11] to the above experimentally obtained values.

Determination of Ionization Constants. The ionization constants of *N*-phenacylimidazole (**42**; $pK_a' = 6.32$ at 22 °C) and *N*-(β-phenyl-β-hydroxyethyl)imidazole (**47**; $pK_a' = 6.68$ at 22 °C) were determined by potentiometric titration according to Albert and Serjeant.[12] Methanolic–aqueous solutions (10^{-3} M) of the hydrochlorides were titrated with 0.02 M KOH using a glass–calomel electrode system on an expanded pH scale. pK_a' values obtained from different methanolic–aqueous mixtures were plotted vs. the corresponding methanol concentration, and extrapolation was made to calculate the pK_a' corresponding to a purely aqueous solution.

Pharmacological Methods. NMRI albino mice of either sex, weighing 20–30 g, were employed for pharmacological studies. The compounds were tested ip and po as aqueous solutions or suspensions in 10% aqueous acacia gum. LD_{50} values were determined in mice both intraperitoneally and orally (10 animals per dose). The mortality rate was recorded over a 7-day period. The animals were also observed for their behaviorial symptoms according to the Irwin scheme.[13] The anticonvulsant activity was evaluated by the maximal electroshock seizure test (MES), using a modification of the method described by E. A. Swinyard.[14] Groups of 10 animals were employed. Maximal seizures were elicited, by a 60-Hz alternating current of 25 mA delivered for 0.2 s via corneal electrodes, 30–60 min after administration. The failure to show tonic–extensor seizures indicated protecting activity. ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[15]

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Synthesis and Antiherpetic Activity of Some 4-[(Aryloxy)alkyl]pyrazoles[1]

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A series of 4-[(aryloxy)alkyl]pyrazoles has been prepared and evaluated in vitro against Herpes simplex virus type 2. Several compounds exhibited minimum inhibitory concentrations in the range of 0.7–6 μg/mL. Some of the more active homologues were evaluated in vivo in the mouse genital model against Herpes simplex virus (HSV) types 1 and 2. At a concentration of 5%, an aqueous solution of compound **3** exhibited a 60% survival rate against HSV-1 and 90% against HSV-2.

We have recently reported on the antiviral evaluation of several series of β-diketones[2-4] and have tested the more promising compounds against Herpes simplex viruses (HSV) in vivo.[5] As an extension of this work, we have

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