ously.[12] Male CD rats, 180–250 g, were fed Purina certified rodent chow (5002) and water ad libitum. 20,25-Diazacholesterol was given intragastrically as a suspension (0.1% Tween 80/saline) at a daily dose of 5 mg/kg for 7 days. Test compounds were administered, as suspensions, intragastrically over the last 4 days of the test. Rats were killed 2 h after the last treatment, the livers were removed, the microsomal fraction was prepared (6×10^6 G/min), and HMG CoA reductase activity was determined for control and treat group rats on the basis of conversion of [^{14}C]-HMG CoA to [^{14}C]mevalonate.[13] All results are presented as percent reduction from concurrent controls. Means were compared to respective controls by Student's t test.

(13) M. S. Brown, S. E. Dana, and J. L. Goldstein, *J. Biol. Chem.*, **249**, 789 (1974).

Acknowledgment. We are grateful to A. J. Damascus, E. Zielinski, and their staff for the spectroscopic and analytical results. We are indebted to K. Williams and T. Lindberg for their assistance in the preparation of additional amounts of compounds.

Registry No. **1d**, 97-62-1; **1f**, 627-90-7; **1j**, 628-97-7; **2d**, 52939-56-7; **2f**, 52939-58-9; **2j**, 52939-55-6; **3b**, 52939-72-7; **3c**, 52939-71-6; **3d**, 52939-65-8; **3e**, 95249-30-2; **3f**, 52939-68-1; **3g**, 95249-31-3; **3h**, 95249-32-4; **3j**, 52939-64-7; **3k**, 95249-33-5; **3l**, 95249-34-6; **3m**, 95249-35-7; **4a**, 73489-84-6; **4b**, 72060-93-6; **4c**, 95249-36-8; **4d**, 95249-37-9; **4e**, 95249-38-0; **4f**, 95249-39-1; **4g**, 95249-40-4; **5a**, 34695-32-4; **5b**, 95249-41-5; **5c**, 95249-42-6; **5d**, 95249-43-7; **6**, 95249-29-9; **7a**, 95249-44-8; **7b**, 95249-45-9; **8a**, 95249-46-0; **8b**, 95249-47-1; **8c**, 95249-48-2; HMGR, 9028-35-7; allyl bromide, 106-95-6.

Effect of Structural Modification of the Hydantoin Ring on Anticonvulsant Activity

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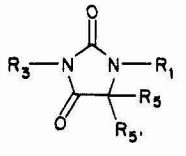
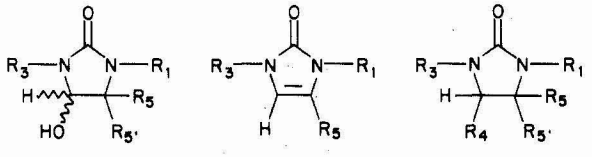
Selectively substituted hydantoins **1** (15 examples), 4-hydroxy-2-imidazolidinones **2** (13 examples), 2-imidazolones **3** (10 examples), 2-imidazolidinones **4** (four examples), vicinal diamines **5** (two examples), and simple amino acid derivatives **6** (four examples) have been prepared and evaluated in the maximal electroshock seizure (MES), subcutaneous pentylenetetrazole seizure threshold (sc Met), and rotorod (Tox) tests. The medium effective doses (ED50) and the medium toxic dose (TD50) for the most active compounds are reported. In general, the most pronounced activity was observed for hydantoins **1** and protected amino acids **6**. Within each series of compounds, enhanced anticonvulsant activity was often noted for compounds containing an aromatic group one carbon removed from a nitrogen atom. Among the most active compounds observed were the amino acid derivative *N*-acetyl-D,L-alanine benzylamide (**6d**) and the two 2-imidazolones 4-methyl-1-(phenylmethyl)-1,3-dihydro-2*H*-imidazol-2-one (**3e**) and 1-phenyl-1,3-dihydro-2*H*-imidazol-2-one (**3g**). Compound **6d** proved to be slightly more potent in the MES test than phenacemide.

Vicinal diamine based substrates form an important set of CNS-active medicinal agents.[2] Among the most important members of this class of compounds are the hydantoins **1**. The effect of structural modification of the hydantoin ring system on biological activity has been a subject of considerable interest.[3] Attention has been focused on the select replacement of the ring atoms and the alteration of the hydrogen bonding properties of the heterocycle.[4]

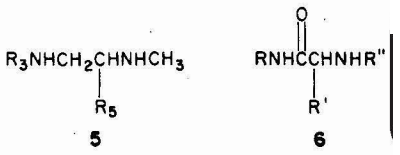


1

In this report, we describe the syntheses, physical properties, and anticonvulsant activities of a select series of hydantoins **1**, 4-hydroxy-2-imidazolidinones **2**, 2-imidazolones **3**, 2-imidazolidinones **4**, vicinal diamines **5**, and amino acid derivatives **6**. This study differed considerably from previous reports in that the basic sequence of atoms (N–C–C–N–C) present in hydantoins **1** has been retained in almost all the substrates examined. Differentiation among the classes of compounds (**1**–**6**) evaluated, however, was achieved by altering the oxidation state, basicity, and lipophilicity of the compounds.



2 **3** **4**



5 **6**

Selection of Compounds. Hydantoins **1a–i** served as the parent compounds in this study (Table I). Within this class of compounds we have systematically varied the R_3 substituent from methyl to benzyl to phenyl and the R_5 group from hydrogen to methyl to phenyl. Identical substituent patterns were incorporated into the 4-

(1) (a) Abstracted from Ph.D dissertation of this author. Additional structure proof, discussion, and experimental and spectral data may be found in this reference. (b) On leave from the University of Mary Hardin-Baylor, Belton, TX 76513, 1982. (c) Camille and Henry Dreyfus Teacher–Scholar Grant Recipient, 1977–1982.

(2) For previous studies, see: Kohn, H.; Kohn, B. A.; Steenberg, M. L.; Buckley, J. P. *J. Med. Chem.* **1977**, *20*, 158–160. Arceneaux, J. H.; Kohn, H.; Steenberg, M. L.; Buckley, J. P. *J. Pharm. Sci.* **1978**, *67*, 600–602.

(3) For a general discussion, see: Jones, G. L.; Woodbury, D. M. *Drug Dev. Res.* **1982**, *2*, 333–355.

(4) Poupaert, J. H.; Vandervorst, D.; Guiot, P.; Moustafa, M. M. M.; Dumont, P. *J. Med. Chem.* **1984**, *27*, 76–78 and references therein.

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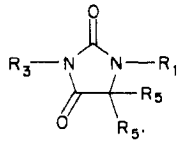
Table I. Pharmacological Evaluation of 2,4-Imidazolidinediones (Hydantoins) 1

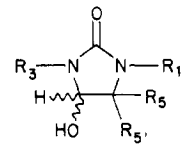


1

	compound				results[a]			
no.	R_1	R_3	R_5	$R_{5'}$	MES[b]	sc Met[c]	Tox[d]	ASP[e]
1a	H	CH_3	H	H	0	0	0	III
1b	H	CH_3	CH_3	H	0	0	0	III
1c	H	CH_3	Ph	H	3	3	1	I
1d	H	Bn[f]	H	H	3	2	2	I
1e	H	Bn[f]	CH_3	H	2	4	1	I
1f	H	Bn[f]	Ph	H	0	0	0	III
1g	H	Ph	H	H	1	0	0	III
1h	H	Ph	CH_3	H	0	0	1	III
1i	H	Ph	Ph	H	0	0	0	III
1j	H	$CH_2Ph(3\text{-}OCH_3)$	CH_3	CH_3	1	0	0	III
1k	H	$(CH_2)_2Ph$	CH_3	CH_3	3	2	2	I
1l	H	$(CH_2)_3Ph(3\text{-}OCH_3)$	CH_3	CH_3	2	1	2	II
1m	H	H	CH_3	H	0	0	0	III
1n	H	H	Ph	H	2	3	1	I
1o	CH_3	CH_3	CH_3	H	0	2	0	II

[a] The following code has been adopted: 0 = no activity at dose levels of 600 mg/kg; 1 = noticeable activity at dose levels of 600 mg/kg; 2 = noticeable activity at dose levels of 300 mg/kg; 3 = noticeable activity at dose levels of 100 mg/kg; 4 = noticeable activity at dose levels of 30 mg/kg. [b] MES = maximal electroshock seizure test. [c] sc Met = subcutaneous pentylenetetrazole (Metrazol) seizure test. [d] Tox = neurologic toxicity (the rotorod test). [e] ASP Results Classification. [f] Bn = benzyl.

Table II. Pharmacological Evaluation of 3-Substituted 4-Hydroxy-2-imidazolidinones 2



2

	compound				results[a]			
no.	R_1	R_3	R_5	$R_{5'}$	MES[b]	sc Met[c]	Tox[d]	ASP[e]
2a	H	CH_3	H	H	0	0	0	III
2b	H	CH_3	CH_3	H	0	0	0	III
2c	H	CH_3	Ph	H	1	2	0	II
2d	H	Bn[f]	H	H	1	0	0	III
2e	H	Bn[f]	CH_3	H	2	1	1	II
2f	H	Bn[f]	Ph	H	0	0	0	III
2g	H	Ph	H	H	0	0	0	III
2h	H	Ph	CH_3	H	1	1	1	III
2i	H	Ph	Ph	H	0	0	0	III
2j	H	$CH_2Ph(3\text{-}OCH_3)$	CH_3	CH_3	1	0	0	III
2k	H	$(CH_2)_2Ph$	CH_3	CH_3	1	1	1	III
2l	H	$(CH_2)_3Ph(3\text{-}OCH_3)$	CH_3	CH_3	2	2	1	II
2o	CH_3	CH_3	CH_3	H	0	0	0	III

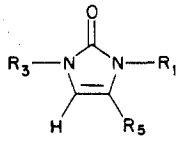
[a] The following code has been adopted: 0 = no activity at dose levels of 600 mg/kg; 1 = noticeable activity at dose levels of 600 mg/kg; 2 = noticeable activity at dose levels of 300 mg/kg; 3 = noticeable activity at dose levels of 100 mg/kg; 4 = noticeable activity at dose levels of 30 mg/kg. [b] MES = maximal electroshock seizure test. [c] sc Met = subcutaneous pentylenetetrazole (Metrazol) seizure test. [d] Tox = neurologic toxicity (the rotorod test). [e] ASP Results Classification. [f] Bn = benzyl.

hydroxy-2-imidazolidinone (**2a–i**) (Table II) and 2-imidazolone (**3a–i**) (Table III) series. We have also examined the pharmacological activity of two carbon-5 monosubstituted hydantoins (**1m** and **n**) (Table I), the more complex N_1,N_3,C_5- and N_3,C_5,C_5-trisubstituted hydantoins **1o** and **1j–l**, respectively (Table I), and the corresponding 4-hydroxy adducts (**2o** and **2j–l**) (Table II) as well as 2-imidazolone **3o** (Table III). Included in our survey were the substituted imidazolidinones **4a–e**, the vicinal diamines **5a** and **5b**, and the amino acid derivatives **6a–d** (Table IV). Of note, the substituent patterns present in **1** have been preserved in these structural derivatives.

Chemistry. The synthetic procedures as well as physical and spectral properties of hydantoins **1a–o**,[5,6] 4-hydroxy-2-imidazolidinones **2a–l** and **2o**,[5,6] 2-imidazolidinones **4b–d**,[6] and vicinal diamines **5a** and **5b**[5] have been previously reported. All the carbon-5 monosubstituted hydantoins **1** as well as diamines **5a** and **5b** were racemic. Pharmacological evaluation of 4-hydroxy-2-imidazolidinones **2b, 2c, 2e, 2f, 2h**, and **2i** was conducted on the synthetic diastereomeric mixture.

(5) Cortes, S.; Kohn, H. *J. Org. Chem.* **1983**, *48*, 2246–2254.
(6) Kohn, H.; Liao, Z. K. *J. Org. Chem.* **1982**, *47*, 2787–2789.

Table III. Pharmacological Evaluation of 3-Substituted 2-Imidazolones **3**



3

	compound			results[a]			
no.	R_1	R_3	R_5	MES[b]	sc Met[c]	Tox[d]	ASP[e]
3a	H	CH_3	H	0	0	0	III
3b	H	CH_3	CH_3	0	0	0	III
3c	H	CH_3	Ph	1	1	0	III
3d	H	Bn[f]	H	3	2	2	I
3e	H	Bn[f]	CH_3	2	2	1	II
3f	H	Bn[f]	Ph	0	0	0	III
3g	H	Ph	H	3	2	2	I
3h	H	Ph	CH_3	1	0	1	III
3i	H	Ph	Ph	0	2	0	II
3o	CH_3	CH_3	CH_3	0	0	0	III

[a] The following code has been adopted: 0 = no activity at dose levels of 600 mg/kg; 1 = noticeable activity at dose levels of 600 mg/kg; 2 = noticeable activity at dose levels of 300 mg/kg; 3 = noticeable activity at dose levels of 100 mg/kg; 4 = noticeable activity at dose levels of 30 mg/kg. [b] MES = maximal electroshock seizure test. [c] sc Met = subcutaneous pentylenetetrazole (Metrazol) seizure test. [d] Tox = neurologic toxicity (the rotorod test). [e] ASP Results Classification. [f] Bn = benzyl.

The 2-imidazolones[7-11] **3** were prepared by the acid-promoted dehydration of the 4-hydroxy-2-imidazolidinones **2**. Key physical and spectral properties for these compounds are listed in Table V.

Imidazolone **3c** was selectively hydrogenated to give **4a** by using palladium on activated carbon (H_2, 40 psi, 40 h) in glacial acetic acid.[12] The methodologies employed for the preparation of each of the racemic amino acid derivatives **6a–d** were patterned after procedures common to peptide synthesis.[13] D,L-Phenylglycine methylamide (**6a**) and D,L-alanine benzylamide (**6c**) were synthesized by treatment of the hydrochloride salt of the corresponding methyl ester[14] with excess methylamine or benzylamine, respectively. Acetylation of **6a** and **6c** with a slight excess of acetic anhydride gave **6b** and **6d**, respectively, as crystalline solids.

Pharmacological Evaluation. The 48 substrates prepared in this study were submitted to the National Institutes of Health Antiepileptic Drug Development Program for pharmacological evaluation. Each compound was tested for anticonvulsant activity in mice by using the procedure described by Krall et al.[15]

The phase I test results are summarized in Tables I–IV. All compounds were administered in four dose levels (30, 100, 300, and 600 mg). The smallest dose that produced activity was noted for separate tests involving maximal electroshock-induced convulsions (MES), subcutaneous Metrazol-induced convulsions (sc Met), and a rotorod toxicity test (Tox). The overall effect of the drug in these three tests was then given by one of four different ratings (ASP Results Classification I–IV). Compounds with ratings of I or II are considered promissory and were considered for phase II (quantification) testing (Table VI). This stage involved the same tests previously described, except under a more strict monitoring of dosages and activity time spans. It also included an evaluation of the median effective dose (ED50) and the median toxic dose (TD50).

Evaluation of the composite set of results revealed significant trends. First, the level of CNS activity decreased as the overall state of oxidation of the molecule was reduced. For the six classes of compounds evaluated, hydantoins **1** and amino acid derivatives **6** were the most active, followed by 4-hydroxy-2-imidazolidinones **2**, 2-imidazolones **3**, and 2-imidazolidinones **4**, followed by vicinal diamines **5**. Second, enhanced anticonvulsant activity was often noted for compounds containing an aromatic group one carbon removed from an amino residue (i.e., **1c–e**, **1n**, **2c**, **2e**, **3d**, **3e**, **3g**, **3i**, **4a**, **4b**, **6c**, and **6d**). Exceptions were observed (i.e., **1k**, **1l**, **1o**, **2l**). Ample precedence exists for this structural pattern. Many compounds which exhibit pronounced CNS depressant activity contain an aromatic group one carbon removed from a diamine linkage.[3,16]

In view of these trends, it was of interest to trace the biological activities of two series of compounds. In the first set (**1e**, **2e**, **3e**, **5b**, **6c** and **6d**) each compound contained both a *N*-benzyl moiety and a methyl group attached to the vicinal diamine linkage. In the second group (**1c**, **2c**, **3c**, **4a**, **5a**, **6a**, and **6b**) the common structural features were a *N*-methyl group and a phenyl moiety attached to the diamine moiety. All the compounds in the former set other than the basic diamine **5b** exhibited significant activity. Compounds **1c** and **6d** were both assigned an ASP classification rating of I. Protected amino acid **6d** can be viewed as the open-chain analogue of hydantoin **1e**.[17] The

(7) Leonard, N. J.; Wiemer, D. F. *J. Am. Chem. Soc.* **1976**, *98*, 8218–8221.
(8) Wilk, I. J.; Close, W. J. *J. Org. Chem.* **1950**, *15*, 1020–1022.
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(12) Duschinsky, R.; Dolan, L. A.; Randall, L. O.; Lehmann, G. *J. Am. Chem. Soc.* **1947**, *69*, 3150.
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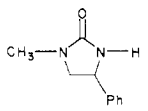
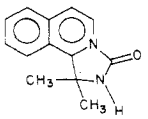
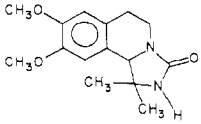
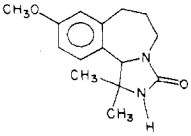
(14) Barfield, M.; Al-Obeidi, F. A.; Hruby, V. J.; Walter, S. R. *J. Am. Chem. Soc.* **1982**, *104*, 3302–3306.
(15) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia* **1978**, *19*, 409–428.
(16) For representative examples, see: Troupin, A. S.; Friel, P.; Wilensky, A. J.; Moretti-Ojemann, L.; Levy, R. H.; Feigl, P. *Neurology* **1979**, *29*, 458–460. Congdon, P. J.; Forsythe, W. I. *Epilepsia* **1980**, *21*, 97–102. Griffith, P. A.; Karp, H. R. *Ann. Neurol.* **1980**, *7*, 493. Pinder, R. M.; Brogden, R. N.; Speight, T. M.; Avery, G. S. *Drugs* **1976**, *12*, 321–361. Ogata, M.; Matsumoto, H.; Hirose, K. *J. Med. Chem.* **1977**, *20*, 776–781.

Table IV. Pharmacological Evaluation of Additional Vicinal Diamine Based Substrates[a]

no.	compd	MES[b]	sc Met[c]	Tox[d]	ASP[e]
4a		2	1	2	II
4b		2	2	2	II
4c		0	0	1	III
4d		0	0	0	III
5a	$CH_3NHCH_2\underset{Ph}{CH}NHCH_3$	0	0	2	III
5b	$BnNHCH_2\underset{CH_3}{CH}NHCH_3$	0	0	2	III
6a	$CH_3NHC(=O)CH(Ph)NH_2$ (dl)	0	0	0	III
6b	$CH_3NHC(=O)CH(Ph)NHC(=O)CH_3$ (dl)	0	0	0	IV
6c	$BnNHC(=O)CH(CH_3)NH_2$ (dl)	2	0	2	II
6d	$BnNHC(=O)CH(CH_3)NHC(=O)CH_3$ (dl)	3	0	1	I

[a] The following code has been adopted: 0 = no activity at dose levels of 600 mg/kg; 1 = noticeable activity at dose levels of 600 mg/kg; 2 = noticeable activity at dose levels of 300 mg/kg; 3 = noticeable activity at dose levels of 100 mg/kg; 4 = noticeable activity at dose levels of 30 mg/kg. [b] MES = maximal electroshock seizure test. [c] sc Met = subcutaneous pentylenetetrazole (Metrazol) seizure test. [d] Tox = neurologic toxicity (the rotorod test). [e] ASP Results Classification. [f] Bn = benzyl.

results observed in the latter set were less straightforward. Significant pharmacological activity was detected for **1c**, **2c**, and **4a**, while **3c**, **5a**, and **6a** were inactive, and the fully protected amino acid **6b** gave inconsistent test results.

The pharmacological activities observed for compounds **1c**, **1d**, **1k**, **1n**, **3d**, **3e**, **3g**, and **6d** warranted their further evaluation in phase II trails. These data are summarized in Table VI along with similar information for several proven antiepileptic drugs.[15,18] Promising results were obtained for compounds **3e**, **3g**, and **6d**. Compound **6d** was found to be slightly more potent in the MES test than phenacemide and equally as toxic. Compounds **3e**, **3g**, and **6d** are slated for additional screening at the National Institutes of Health.

Experimental Section

General Methods. Melting points were determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Beckman IR-4250 spectrophotometer and calibrated against the 1601-cm^{-1} band of polystyrene. Absorption values are expressed in wavenumbers (cm^{-1}). Proton nuclear magnetic resonance (^1H NMR) spectra were recorded on Varian Associates Models T-60 and FT-80A NMR spectrometers. Carbon nuclear magnetic resonance (^{13}C NMR) spectra were run on a Varian Associates Models FT-80A instrument. Chemical shifts are in parts per million (δ values) relative to Me_4Si, and coupling constants (J values) are in hertz. Mass spectral data were obtained at an ionizing voltage of 70 eV on a Hewlett-Packard 5930 gas chromatograph–mass spectrometer. High-resolution (EI mode) mass spectra were performed by Dr. James Hudson at the Department of Chemistry, University of Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70 eV. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, MI.

The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. All anhydrous reactions were run under nitrogen, and all glassware was dried before use.

Preparation of 2-Imidazolones (3). General Procedure. To a suspension of the 4-hydroxy-2-imidazolidinone **2** (6.1–15.8 mmol) in CH_2Cl_2 (200 mL) or CH_2Cl_2–MeOH (200 mL, 10–100/1, v/v) was added two drops of TFA and the mixture stirred (30 min) at room temperature. During this time interval, the initially heterogeneous system became a clear solution. Evaporation of the solvent in vacuo afforded the desired 2-imidazolone. Spectral (^1H and ^{13}C NMR) analyses indicated that the material was essentially pure.

Purification was accomplished in the case of **3a** by recrystallization from dichloromethane–hexanes, **3b** by sublimation (70 °C, 0.1 torr), **3c** by recrystallization from EtOH, **3d** by recrystallization from dichloromethane–hexanes, **3e** by recrystallization from benzene–methanol, **3f** by recrystallization from EtOH–CH_2Cl_2 or sublimation (168 °C, 0.14 torr), and **3g** and **3h** by recrystallization from benzene.

Preparation of 1-Methyl-4-phenyl-2-imidazolidinone (4a). To a glacial HOAc solution (40 mL) of **3c** (1.70 g, 98 mmol) in a thick-wall glass bottle was added Pd–C (Pd content 1%, 1.00 g). The container was connected to a medium-pressure hydrogenation apparatus and the resulting mixture stirred under H_2 (40 psi) for 40 h. The catalyst was filtered with the aid of a Celite pad, and the filtrate was neutralized (pH ~8) with aqueous 5 N NaOH and then extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Recrystallization from CH_2Cl_2–hexanes gave 1.00 g (58%) of **4a**: mp 134.5–136.0 °C; IR (CH_2Cl_2) 1715 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (s, 3 H), 3.12 (d, d, J = 7.4, 8.6 Hz, 1 H), 3.71 (d, d, J = 8.6, 8.8 Hz, 1 H), 4.69 (d, d, J = 7.4, 8.8 Hz, 1 H), 6.08 (br s, 1 H), 7.31 (s, 5 H); ^{13}C NMR ($CDCl_3$) 30.5, 53.6, 56.1, 126.0, 128.0, 128.8, 141.9, 162.5 ppm; mass spectrum, m/e (relative intensity) 176 (100), 175 (37), 104 (28). Anal. ($C_{10}H_{12}N_2O$) C, H, N.

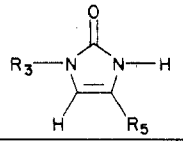
D,L-Phenylglycine Methylamide (6a). A 40% aqueous solution of methylamine (60 mL, 0.70 mol) was slowly added to D,L-phenylglycine methyl ester hydrochloride[14] (9.00 g, 44.7 mmol). The resulting solution was heated to reflux (3 h) and then extracted with $CHCl_3$ (3 × 50 mL). The organic layers were combined, dried (Na_2SO_4), and concentrated in vacuo. Purification of the oily residue by short-path distillation (100 °C, 0.5 torr) gave 4.60 g (63%) of **6a**: IR (neat, NaCl) 3310, 1665, 1550 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.85 (s, 2 H), 2.64 (d, J = 5.0 Hz, 3 H), 4.35 (s, 1 H), 7.26 (s, 5 H), 7.35–7.60 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 25.9, 59.6, 126.8, 127.6, 128.6, 141.6, 173.9 ppm; mass spectrum (CI mode), m/e 165 (P + 1). Anal. ($C_9H_{12}N_2O$) C, H, N.

***N*-Acetyl-D,L-phenylglycine Methylamide (6b).** Acetic anhydride (2.90 g, 28 mmol) was added dropwise to **6a** (3.40 g, 20 mmol) and the mixture allowed to stir at room temperature (1.5 h). During this time, a copious white precipitate formed. This material was collected by filtration, dried in vacuo, and recrystallized from absolute alcohol to give 2.00 g (49%) of **6b**: mp 232–235 °C dec; IR (KBr) 3310, 1645 cm^{-1}; ^1H NMR (Me_2SO-d_6) δ 1.89 (s, 3 H), 2.58 (d, J = 4.6 Hz, 3 H), 5.42 (d, J = 8.1 Hz, 1 H), 7.35 (s, 5 H), 8.18 (br q, J = 4.2 Hz, 1 H), 8.47 (d, J = 8.1 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) 22.4, 25.5, 56.3, 127.1, 127.3, 128.1, 139.0, 168.9, 170.3 ppm; mass spectrum (CI mode), m/e 207 (P + 1). Anal. ($C_{11}H_{14}N_2O_2$) C, H, N.

(17) Although amino acid derivatives **6a–d** structurally resemble phenacemide analogues,[3] the sequence of atoms in these two classes of compounds differ.

(18) Results obtained by Dr. Gill D. Gladding (ASP Project) of the National Institute of Neurological and Communicative Disorders and Stroke at the National Institutes of Health (private communication).

Table V. Summary of Selected Physical and Spectral Properties of 2-Imidazolone Derivatives **3**[a]



no.	R^3	R^5	yield, %	mp, °C	IR data,[b] C=O	^{1}H NMR data,[c] C^4 H	^{13}C NMR data[c] C^2=O	C^4	C^5
3a	CH_3	H	28	141–142[d]	1670	6.16	155.0	108.3	112.6
3b	CH_3	CH_3	24	*e, f*	1680	5.84	155.1	108.2	117.9
3c	CH_3	Ph	38	268–278 dec[g]	1690	6.98	153.8	109.5	120.3
3d	Bn[h]	H	51	134–136[i]	1680	6.09	155.0	108.8	111.2
3e	Bn[h]	CH_3	68	158–161[j]	1670	5.77	154.9	106.9	118.4
3f	Bn[h]	Ph	32	247–254 dec[f]	1690	7.05	153.7	108.4	120.9
3g	Ph	H	59	136–139[k]	1680	6.41	153.8	109.7	111.0
3h	Ph	CH_3	17	169–172[l]	1680	6.23	153.7	106.5	119.5
3i	Ph	Ph	15	180–182[f,m]	1690	6.86	153.9	106.3	124.0

[a] See reference 5 for a detail description of the physical properties of **3m**. [b] Infrared were taken in KBr disks (in cm^{-1}). [c] NMR spectra were taken in $CDCl_3$ or Me_2SO-d_6 (in δ). [d] Lit.[7] mp 139–140 °C. [e] Hygroscopic sample. [f] Elemental composition verified by high-resolution mass spectroscopy. [g] Lit.[8] mp 275–278 °C. [h] Bn = benzyl. [i] Lit.[9] mp 133–135 °C. [j] Lit.[10] mp 162–165 °C. [k] Lit.[11] mp 123 °C. [l] Lit.[10] mp 170 °C. [m] Lit.[10] mp 215–216 °C.

Table VI. Summary of Phase II Evaluation

no.	Tox TD50[a]	MES ED50[a]	sc Met ED50[a]
1c	271 (223–326)	75 (60–88)	26 (16–36)
1d	224 (179–288)	65 (53–82)	114 (88–149)
1k	243 (212–268)	110 (90–131)	130 (101–154)
1n	399 (341–472)	156 (129–183)	109 (85–137)
3d	190 (176–203)	83 (71–94)	90 (53–158)
3e	268 (229–309)	90 (83–98)	*b*
3g	211 (194–239)	124 (103–141)	173 (156–195)
6d	454 (417–501)	77 (67–89)	*b*
phenytoin[c]	66	10	*d*
mephenytoin[c]	154	61	31
phenacemide[e]	421 (337–549)	87 (74–100)	116 (71–150)

[a] Numbers in parentheses are 95% confidence intervals. [b] The ED50 value was not computed for this substrate. [c] Reference 18. [d] Not effective. [e] Reference 15.

D,L-Alanine Benzylamide (6c). Benzylamine (30.68 g, 0.29 mol) was added dropwise to a stirred solution of D,L-alanine methyl ester hydrochloride (20.00 g, 0.14 mol) in methanol (50 mL). The mixture was heated to reflux (3 h) and concentrated in vacuo, and the residue was triturated with $CHCl_3$ (3 × 50 mL). The remaining solid was dissolved in aqueous 5% NaOH and extracted with $CHCl_3$ (3 × 50 mL). All the organic layers were combined, dried (Na_2SO_4), concentrated in vacuo, and distilled (twice) by using a short-path distillation apparatus (100 °C, 0.5 torr) to yield 5.50 g (22%) of product: IR (neat, NaCl) 3300, 1655, 1525 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.34 (d, J = 7.0 Hz, 3 H), 1.58 (s, 2 H), 3.51 (q, J = 7.0 Hz, 1 H), 4.42 (d, J = 5.9 Hz, 2 H), 7.27 (s, 5 H), 7.39 (br s, 1 H); ^{13}C NMR ($CDCl_3$) 21.8, 43.1, 50.8, 127.4, 127.7, 128.7, 138.6, 175.6 ppm; mass spectrum (CI mode), m/e 179 (P + 1); mass spectrum, m/e (relative intensity) 179 (5), 178 (3), 177 (6), 106 (29), 91 (100), 65 (20). Anal. ($C_{10}H_{14}N_2O$) C, H, N.

***N*-Acetyl-D,L-alanine Benzylamide (6d).** Acetic anhydride (2.20 g, 0.022 mol) was slowly added to a CH_2Cl_2 solution (30 mL) of **6c** (3.80 g, 0.021 mol) and allowed to stir at room temperature (3 h). The mixture was then successively washed with H_2O (15 mL), 1% aqueous NaOH (15 mL), and H_2O (15 mL), dried (Na_2SO_4), and concentrated in vacuo. The residue was recrystallized from CH_2Cl_2 to yield 2.50 g (54%) of **6d**: mp 239–241 °C; IR ($CHCl_3$) 3440, 3300, 3005, 1660, 1515 cm^{-1}; ^{1}H NMR (Me_2SO-d_6) δ 1.22 (d, J = 7.1 Hz, 3 H), 1.84 (s, 3 H), 4.04–4.50 (m, 3 H), 7.26 (s, 5 H), 8.11 (br d, J = 7.3 Hz, 1 H), 8.42 (br t, J = 6 Hz, 1 H); ^{13}C NMR (Me_2SO-d_6) 18.2, 22.4, 41.9, 48.2, 126.5, 126.9, 128.1, 139.4, 168.9, 172.4 ppm; mass spectrum (CI mode), m/e 221 (P + 1); M_r 220.1208 (calcd for $C_{12}H_{16}N_2O_2$, 220.1212).

Pharmacology. Each compound listed in Tables I–IV was tested for anticonvulsant activity (phase I evaluation) with use of male Carworth Farms No. 1 mice. All compounds were given in four dose levels (30, 100, 300, and 600 mg). Seizures were then artificially induced by either electroshock or pentylenetetrazole. Maximal electroshock seizures (MES) are elicited with a 60-cycle alternating current of 50-mA intensity (5–7 times that necessary to elicit minimal electroshock seizures) delivered for 0.2 s via corneal electrodes. A drop of 0.9% saline is instilled in the eye prior to application of the electrodes so as to prevent the death of the animal. Protection in this test is defined as the abolition of the hind limb tonic extension component of the seizure. The subcutaneous pentylenetetrazole (Metrazol) seizure threshold test (sc Met) entailed the administration of 85 mg/kg of pentylenetetrazole as a 0.5% solution subcutaneously in the posterior midline. This amount of pentylenetetrazole is expected to produce seizures in greater than 95% of mice. The animal is observed for 30 min. Protection is defined as the failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5-s duration). The effects of the compounds on forced and spontaneous motor activity were evaluated in mice by the rotorod test (Tox). The animal is placed on an 1-in.-diameter knurled plastic rod rotating at 6 rpm after the administration of the drug. Normal mice can remain on a rod rotating at this speed indefinitely. Neurologic toxicity is defined as the failure of the animal to remain on the rod for 1 min. The MES and sc Met tests were conducted on single animals while four mice were utilized for the Tox test.

The overall effect of the drug in these three tests is then given by one of four different ratings (ASP Results Classification I–IV). The number I indicated anticonvulsant activity at 100 mg/kg or less, II designated activity at doses greater than 100 mg/kg, III denoted no anticonvulsant activity at doses up to and including 300 mg/kg, and IV indicated that anticonvulsant activity and toxicity or toxicity alone was demonstrated at 30 mg/kg or that anticonvulsant activity was displayed at 100 mg/kg or less, but that the test results were not consistent.

Compounds with ratings of I and II are considered promissory and were considered for phase II (quantification) testing. The dose–effect behavior of the eight substrates listed in Table VI was evaluated by using the previously described procedures by the administration of varying dose levels of each compound, treating normally eight mice at each dose.

Acknowledgment. We are grateful to Dr. Gill D. Gladding and the Anticonvulsant Screening Project (ASP) of the National Institute of Neurological and Communicative Disorders and Stroke at the National Institutes of Health for kindly performing all the pharmacological studies. Funds for this project were provided by the National Institutes of Health.

Registry No. **1a**, 6843-45-4; **1b**, 74310-97-7; **1c**, 93860-68-5; **1d**, 2301-40-8; **1e**, 93781-89-6; **1f**, 93781-90-9; **1g**, 2221-13-8; **1h**, 93781-91-0; **1i**, 93781-92-1; **1j**, 81572-14-7; **1k**, 93781-93-2; **1l**, 81572-15-8; **1m**, 67337-69-3; **1n**, 27534-86-7; **1o**, 93781-94-3; **2a**, 85369-76-2; **2b**, 93781-95-4; **2c**, 93781-96-5; **2d**, 85369-80-8; **2e**, 92764-01-7; **2f**, 93781-97-6; **2g**, 85369-84-2; **2h**, 93781-98-7; **2i**,

93781-99-8; **2j**, 81572-18-1; **2k**, 93782-00-4; **2l**, 81572-19-2; **2o**, 93782-01-5; **3a**, 39799-77-4; **3b**, 93782-02-6; **3c**, 93782-03-7; **3d**, 67909-04-0; **3e**, 33542-53-9; **3f**, 93782-04-8; **3g**, 53995-06-5; **3h**, 24631-04-7; **3i**, 2032-07-7; **3o**, 24138-94-1; **4a**, 93782-05-9; **4b**, 81572-20-5; **4c**, 81583-49-5; **4d**, 81572-22-7; **5a**, 93860-69-6; **5b**, 93782-06-0; **6a**, 93782-08-2; **6b**, 93782-08-2; **6c**, 93860-70-9; **6d**, 93782-09-3; D,L-phenylglycine methyl ester hydrochloride, 15028-40-7; D,L-alanine methyl ester hydrochloride, 13515-97-4.

1-[3-(Diarylamino)propyl]piperidines and Related Compounds, Potential Antipsychotic Agents with Low Cataleptogenic Profiles

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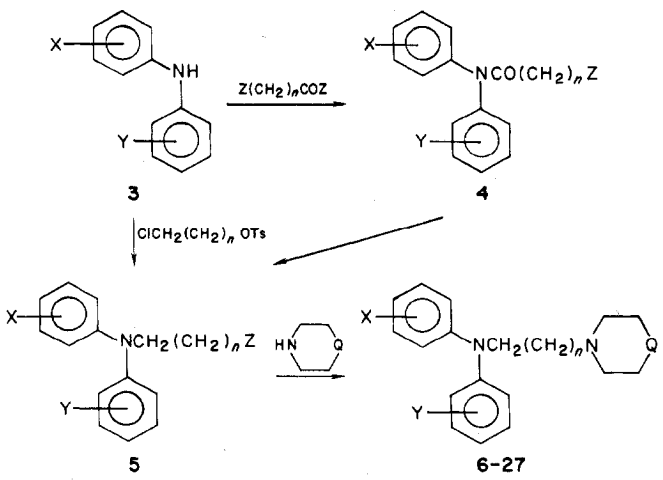
On the basis of a structural model of the postsynaptic dopaminergic antagonist pharmacophore, a series of 1-[3-(diarylamino)propyl]piperidines and related compounds was synthesized and evaluated for potential antipsychotic activity. For a rapid measure of activity, the target compounds were initially screened in vitro for inhibition of [^{3}H]haloperidol binding and in vivo in a test of locomotor activity. Behavioral efficacy of compounds identified from the initial screens was more accurately measured in rats by using a suppression of high base-line medial forebrain bundle self-stimulation test model. The propensity of these compounds for causing extrapyramidal side effects was evaluated by using a rat catalepsy method. On the basis of these test models, we have shown that the methine carbon of the 1-(4,4-diarylbutyl)piperidines can be advantageously replaced with a nitrogen atom. The 1-[3-(diarylamino)propyl]piperidines were less cataleptic than the corresponding 1-(4,4-diarylbutyl)piperidines. The compounds with the widest separation between efficacious dose and cataleptic dose are 8-[3-[bis(4-fluorophenyl)amino]propyl]-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one (**6**), 1-[1-[3-[bis(4-fluorophenyl)amino]propyl]-4-piperidinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**11**), 1-[1-[3-[bis(4-fluorophenyl)amino]propyl]-1,2,3,6-tetrahydro-4-pyridinyl]-1,3-dihydro-2*H*-benzimidazol-2-one (**22**), and 1-[3-[bis(4-fluorophenyl)amino]propyl]-4-(2-methoxyphenyl)piperazine (**26**).

In the past 25 years, the advent of antipsychotic drugs has resulted in a virtual revolution in the treatment of schizophrenia.[1] Although these agents have proven beneficial, their therapeutic effects are accompanied by distinct disadvantages including extrapyramidal side effects (EPS) and tardive dyskinesia (TD).[2] At one time, in fact, EPS was actually considered by many investigators as evidence of therapeutic efficacy. With the discovery of newer agents, sometimes described as atypical antipsychotic drugs, it has been suggested that the side effects (EPS and TD) could be separated from the therapeutic effects.[3] For example, the atypical antipsychotic agent, clozapine has been reported to be both effective and free of EPS in clinical studies although other problems have kept it from the market place.[4]

Therefore, the development of a compound for the treatment of schizophrenia with minimal EPS would represent a significant therapeutic improvement over existing drugs. This report summarizes some of the efforts from our laboratories directed toward this goal.

Studies of the structural features of the various classes of postsynaptic dopamine receptor antagonists used as antipsychotic agents have led investigators to identify a common pharmacophore responsible for their activities.[5] Two series of compounds incorporating this pharmacophore are the 1-[4,4-bis(4-fluorophenyl)butyl]piperidines and the phenothiazines typified by pimozide (**1**) and chlorpromazine (**2**), respectively. On the basis of the structural features of these two series of compounds, we became interested in the structure–activity relationships (SAR) of the [(diarylamino)alkyl]piperidines and -piperazines **6–27**, which may be thought of as arising through either replacement of the methine carbon atom of the 1-(4,4-diarylbutyl)piperidine structure with a tertiary nitrogen atom or elimination of the bridged sulfur atom from the phenothiazine moiety. The goal was to identify com-

Scheme I



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