Anal. Calcd for $C_{17}H_{14}N_2O \cdot 0.25H_2O$: C, 76.52; H, 5.48; N, 10.52. Found: C, 76.78; H, 5.49; N, 10.40.

5-Formyl-11-methyl-6*H*-pyrido[4,3-*b*]carbazole (17-Oxoellipticine) (47). A suspension of 40 mg of the carbinol 46 and 200 mg of MnO_2 in 35 mL of $CHCl_3$ was heated under reflux for 3.5 h. The hot suspension was filtered and the collected solid was washed with $CHCl_3$. The combined filtrates were evaporated to dryness to leave a residue, which was chromatographed on silica gel. Elution with EtOAc furnished 23 mg of the desired aldehyde 48, which melted at 274–276 °C (lit.[34] mp 275–276 °C) after crystallization from $CHCl_3$–hexane. The IR spectrum was identical in all respects with that of an authentic sample.[34] Further elution of the column with EtOAc–MeOH (19:1) gave 11 mg of recovered starting material.

5-(Hydroxymethyl)-11-methyl-6*H*-pyrido[4,3-*b*]carbazole *N*-Methylcarbamate (48). To a solution of 400 mg (1.53 mmol) of the carbinol 46 in 25 mL of dry pyridine and 20 mL of reagent grade acetone there was added 900 μL of MeNCO. The solution was magnetically stirred at room temperature in a stoppered flask until all the starting alcohol had disappeared as judged by TLC (ca. 3 days). The solvents were removed in vacuo, and the residue was crystallized from EtOAc–CH_2Cl_2–MeOH to give 152 mg of the desired carbamate, mp 213–214.5 °C. The filtrate was concentrated to dryness and the remaining solid was flash chromatographed to give an additional 145 mg of material of similar purity: wt 307 mg (61%); NMR (Me_2SO-d_6) δ 11.62 (s, 1 H), 9.71 (s, 1 H), 8.46 (d, 1 H), 8.39 (d, 1 H), 7.97 (d, 1 H), 7.61–7.54 (m, 2 H), 7.32–7.29 (m, 1 H), 7.04 (d, 1 H), 5.77 (s, 2 H), 3.34 (s, 3 H), 2.60 (s, 3 H). Anal. ($C_{19}H_{17}N_3O_2$) C, H, N.

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6-Alkoxy-*N*,*N*-disubstituted-2-pyridinamines as Anticonvulsant Agents

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The anticonvulsant effect of a series of 6-alkoxy-*N*,*N*-disubstituted-2-pyridinamines is described. An investigation was carried out to optimize the activity/side-effect ratio in this series of compounds. The most desirable profile was seen with 1-[6-(2-methylpropoxy)-2-pyridinyl]piperazine, 6, and this compound was selected for a more complete pharmacological evaluation. Overall, 6 has a pharmacological profile that is very similar to that of diphenylhydantoin (phenytoin). While nearly equipotent to phenytoin, animal studies suggest a fairly short duration of action. In addition, 6 exhibited some troublesome side effects including central nervous system depression and hypothermia.

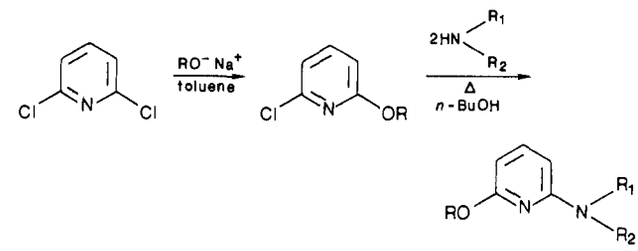
The need for improved agents for the treatment of seizure disorders is widely recognized[1] since currently available antiepileptic drugs are effective in only 60–80% of patients. While absence (petit mal) seizures are well treated in most instances, significant therapeutic improvement is necessary for the treatment of partial-complex (focal) seizures and generalized tonic-clonic (grand mal) epilepsy.[2]

Most marketed anticonvulsants suffer from a broad range of undesirable side effects[3] such as sedation, teratogenicity, cognitive dulling, blood dyscrasia, and liver damage. Failure to achieve control of seizures is frequently due to use-limiting side effects seen with increasing doses of the drugs before a satisfactory therapeutic dose is reached.

Precise mechanisms by which most clinically available anticonvulsants act are unknown.[2a] However, current theories generally agree that several control mechanisms function in normal neuronal tissues and loss of these inhibitory mechanisms causes excitatory mechanisms (that are necessary for normal neuronal function) to "run away" in an uncontrolled neuronal discharge. The result is synchronized and spreading waves of excitation resulting in seizures. Potentially, anticonvulsants could operate by any number of mechanisms that would limit uncontrolled discharges. Consequently, compounds from a wide range of structural classes are known to exhibit anticonvulsant activity.[4] Among these are hydantoins, succinimides, ureas, benzodiazepines, and amides.

Through our drug discovery program and in collaboration with the NIH–NINCDS Antiepileptic Drug Discovery Program,[5] we have recently discovered the anticonvulsant effects of a series of 6-alkoxy-*N*,*N*-disubstituted-2-pyridinamines.

Scheme I



Various 1-(6-alkoxy-2-pyridinyl)piperazines have been reported in the patent and medicinal chemistry literature. Compound 3 (Table I), 1-(6-methoxy-2-pyridinyl)-piperazine, has been reported as an intermediate in the preparation of analgesic, antianaphylactic, antihypertensive, antiinflammatory, broncholytic, central nervous system (CNS) depressant and stimulant, contraceptive, tranquilizing and vasodilatory agents. The active agents

† Department of Chemistry.
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(1) (a) Coatsworth, J. J. *NINCDS Monograph No. 12*; Government Printing Office: Washington, DC, 1971. (b) Porter, R. J.; Penry, J. K. *Advances in Epileptology, 1977: Psychology, Pharmacotherapy and New Diagnostic Approaches*; Meinardi, H., Rowan, A. J., Eds.; Swets and Zeitlinger: Amsterdam, 1978; p 220.
(2) (a) Gallagher, B. B. In *Anticonvulsants*; Vida, J. A., Ed.; Academic: New York, 1977; p 11. (b) Wilder, B. J.; Bruni, J. *Seizure Disorders—A Pharmacological Approach to Treatment*; Raven: New York, 1981; pp 1, 23.
(3) (a) Booker, H. E. *Epilepsia (N.Y.)* **1975**, *16*, 171. (b) Eadie, M. J. *The Treatment of Epilepsy*; Tyrer, J. H., Ed.; MTP: Lancaster, 1980; p 129. (c) Schmidt, D. In *Antiepileptic Drugs, Handbook of Experimental Pharmacology*; Frey, H.-H., Janz, D., Ed.; Springer Verlag: Berlin, 1985; Vol. 74, p 791. (d) Schmidt, D.; Seldon, L. *Adverse Effects of Antiepileptic Drugs*; Raven: New York, 1982; p 3.
(4) Murray, W. J.; Kier, L. B. in ref 2a, p 578.
(5) Kupferberg, H. J.; Gladding, G. D.; Swinyard, E. A. in ref. 3c, p 341.

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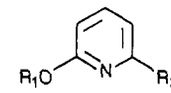
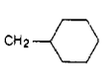
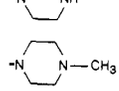
Table I. Structure/Anticonvulsant Activity of 6-Alkoxy-*N*,*N*-disubstituted-2-pyridinamines



no.	R_1	R_2	mp, °C	yield,[a] %	molecular formula[b]	minimum effective dose[c] (MED), mg/kg	minimum ataxic dose[d] (MAD), mg/kg
1			166–169	40	$C_{15}H_{23}N_3O\cdot HCl\cdot 0.5H_2O$	30	10
2	H		200–202	65	$C_9H_{13}N_3O$	>300	>300
3	CH_3		182–184	71	$C_{10}H_{15}N_3OHCl\cdot 0.5H_2O$	30	10
4	CH_2CH_3		166–167	50	$C_{11}H_{17}N_3O\cdot HBr$	30	10
5	$CH(CH_3)_2$		198–201	37	$C_{12}H_{19}N_3O\cdot HCl$	30	<10
6	$CH_2CH(CH_3)_2$		158–159	62	$C_{13}H_{21}N_3O\cdot HCl$	10	30
7			195–197	68	$C_{13}H_{19}N_3O\cdot 2.1HCl$	10	10
8				65	$C_{16}H_{25}N_3O$	30	30
9	$(CH_2)_2N(CH_3)_2$		232–235	14	$C_{13}H_{22}N_4O\cdot 2HCl$	>300	>300
10	$CH_2CH(CH_3)_2$		207–208	72	$C_{14}H_{23}N_3O\cdot HCl$	30	30
11	$CH_2CH(CH_3)_2$		125–128[e]	52	$C_{14}H_{22}N_2O$	>300	>300
12	$CH_2CH(CH_3)_2$		105–108[e]	77	$C_{13}H_{20}N_2O_2$	300	300
13	$CH_2CH(CH_3)_2$	$N(CH_2)_2N(CH_3)_2$	95–98[e]	53	$C_{13}H_{23}N_3O$	100	300
14	$CH_2CH(CH_3)_2$		158–161	61	$C_{14}H_{23}N_3O\cdot 0.1H_2O\cdot 1.3HCl$	30	100

[a] Isolated yields. [b] Satisfactory analytical data ± 0.4% obtained for all compounds; satisfactory halogen analysis for compounds **6**, **7**, **10**, 14, and satisfactory water analysis (Karl Fischer) for compounds **3** and 14. [c] Dose level (10, 30, 100, 300, >300 mg/kg) at which two or more mice (n = 5) were protected against tonic extension produced by maximal electroshock (MES) at 30 min postadministration. [d] Lowest dose level (10, 30, 100, 300, >300 mg/kg) at which two or more mice (n = 5) fell off inverted screen at 30 min postadministration. [e] Boiling point at 0.1 torr.

are formed by attachment (via an appropriate spacer) of various groups such as coumarins,[6] benzodioxazoles,[7] and heterocyclic containing amides[8] to the secondary amine of the piperazine ring.

1-(6-Alkoxy-2-pyridinyl)piperazines with an additional substituent placed at the 3-position of the pyridine ring have been reported to have anorectic activity.[9] 1-(5-Alkoxy-2-pyridinyl)piperazines have been described as selective α_2-adrenergic receptor antagonists useful as antidepressant agents,[10] and 4-(6-alkoxy-2-pyridinyl)-*N*-substituted-1-piperazinamines are known to possess anorexigenic activity.[11]

To our knowledge no member of this chemical class has been reported to possess anticonvulsant activity. Initially we observed that 1-[6-(cyclohexyloxy)-2-pyridinyl]-piperazine, **1** (Table I), was active against seizures induced by maximal electroshock (MES), an accepted model for generalized tonic-clonic seizures.[12] Because the anticonvulsant effect of this compound was accompanied by behavioral neurotoxicity (ataxia), we systematically examined a series of 6-alkoxy-*N*,*N*-dialkyl-2-pyridinamines with the aim of improving the anticonvuslant/neurotoxicity profile exhibited by **1**.

Chemistry

The target molecules were prepared via a two-step synthetic sequence as illustrated in Scheme I. The

(6) Regnier, G.; Carevari, R.; Laubie, M.; Poignant, J. C. German Patent 2 415 082, 1973; *Chem. Abstr.* **1973**, *82*, 4307*w*.

(7) (a) Regnier, G.; Carevari, R.; Laubie, M.; Poignant, J. C. German Patent 2 316 920, 1973; *Chem. Abstr.* **1971**, *80*, 14960*b*. (b) Science Union et Cie.–Societe Francaise de Recherche Medicale Japanese Patent 74-72-270, 1974; *Chem. Abstr.* **1976**, *85*, 63050*s*. (c) Science Union et Cie.–Societe Francaise de Recherche Medicale Japanese Patent 74-72-271, 1974; *Chem. Abstr.* **1976**, *85*, 63049*y*. (d) Regnier, G.; Carevari, R. Canadian Patent 983 493, 1976; *Chem. Abstr.* **1976**, *85*, 46751*d*. (e) Regnier, G.; Carevari, R. Canadian Patent 979 894, 1975; *Chem. Abstr.* **1975**, *84*, 180295*r*.

(8) (a) Science Union et Cie.–Societe Francaise de Recherche Medicale Japanese Patent 74-76-886, 1974; *Chem. Abstr.* **1976**, *85*, 63091*f*. (b) Regnier, G.; Carevari, R. Canadian Patent 985 683, 1976; *Chem. Abstr.* **1976**, *85*, 46755*h*. (c) Regnier, G.; Carevari, R.; Duhault, J. German Patent 2 222 934, 1972; *Chem. Abstr.* **1969**, *78*, 58466*h*. (d) Regnier, G. L.; Carevari, R. J.; Duhalt, J. L.; Laubie, M. L. *Arzneim.-Forsch.* **1974**, *24*, 64.

(9) Lumma, W. C., Jr.; Saari, W. S. German Patent 2 742 509, 1978; *Chem. Abstr.* **1980**, *89*, 43499*z*.

(10) Saari, W. S. U.S. Patent 4 442 103, 1984; *Chem. Abstr.* **1984**, *101*, 60140*j*.

(11) Nisato, D.; Carminati, P. European Patent 21 973, 1981; *Chem. Abstr.* **1981**, *94*, 156769*j*.

(12) (a) Koella, W. P. in ref 3c, p 285. (b) Swinyard, E. A. *Experimental Models of Epilepsy—A Manual for the Laboratory Worker*; Purpura, D. P., Penry, J. K., Woodbury, D. M., Tower, D. B., Walter, R. D., Eds.; Raven: New York, 1972, p 433.

starting material was commercially available 2,6-dichloropyridine. Reaction of a sodium alkoxide (prepared from the appropriate alcohol and sodium metal) with 2,6-dichloropyridine affords the 2-alkoxy-6-chloropyridine. After purification, this material was reacted with 2 molar equiv of the N,N-disubstituted amino compound in 1-butanol to give the desired derivatives.

Results

Compound 1 was initially evaluated in our models of efficacy and behavioral side effects as described in the Experimental Section and was found to cause ataxia at doses considerably lower than those affording protection from electroshock induced seizures (Table I). At the effective dose the activity was short-acting with ataxia remaining after the anticonvulsant effect disappeared. Because the anticonvulsant potency compared favorably with that of known anticonvulsant agents, we began an investigation hoping to increase both the absolute potency and the ratio between the doses showing anticonvulsant activity and behavioral side effects (protective index).

The title compounds can be logically divided into three structural regions: the pyridine ring, the alkoxy side chain, and the *N,N*-dialkyl group. We chose to retain the pyridine nucleus and vary the substituents attached to the 2- and 6-positions of the ring in succession.

We began by retaining the 1-(2-pyridinyl)piperazine portion of the molecule and varying the alkoxy group at the 6-position. Each of the compounds prepared was tested for anticonvulsant activity in the maximal electroshock test and for behavioral side effects in the inverted screen test (see Experimental Section).

The 6-hydroxy derivative **2** was ineffective in preventing seizures caused by maximal electroshock and showed no signs of behavioral toxicity at the highest dose tested (Table I). This suggests that **2**, which exists primarily as the 2-pyridone, is not gaining access to the CNS in contrast to **1**, which contains the lipophilic cyclohexyl ring. Therefore, we systematically increased the size and lipophilicity of the alkoxy side chain.

The ability of the 6-methoxy analogue **3** to enter the CNS was evidenced by the long-lasting ataxia seen at low doses. Seizure protection was not seen until higher doses, giving an unacceptable protective index.

Increasing the alkoxy side chain by one methylene group afforded **4**, whose activity/ataxia profile changed little from that of **3**. Introduction of branching in the alkoxy group gave **5**, which displayed weak anticonvulsant effects at low doses but an inadequate separation between effective and ataxic doses.

Evaluation of the 6-methylpropoxy compound **6** gave the first derivative showing an acceptable protective index.

Thus far, our observations suggested that at least one methylene group should separate a branched chain carbon atom from the oxygen on the pyridine ring. Therefore, the 6-methylpropoxy group of **6** was retained and we explored the effect of restricting the conformational freedom of the two methyl groups in the 6-methylpropoxy chain by forming a cyclopropyl ring, **7**, and a cyclohexyl ring, **8**. In both **7** and **8**, the anticonvulsant activity paralleled the side effects both in duration and severity.

In order to explore the effect of introducing a heteroatom, the secondary carbon atom of the side chain of **6** was replaced by a nitrogen to afford **9**. This modification resulted in the total loss of activity and ataxia, suggesting a lack of accessibility to the CNS.

The 6-methylpropoxy group in the 6-position of the pyridine ring gave the best activity/side effect profile yet seen. We next began selective adjustments to the piperazine ring while retaining the 6-(2-methylpropoxy)pyridine portion of the molecule.

Piperazine alkylation provided **10**, which exhibited short-lasting anticonvulsant activity (less potent than **6**) accompanied by ataxia, suggesting that the terminal nitrogen of the piperazine ring cannot be alkylated and retain optimal activity. The necessity of both piperazine nitrogen atoms was demonstrated by the lack of activity of **11** and **12**.

The importance of holding both nitrogens in a fixed relationship as found in the piperazine ring was next examined. All animals were protected from seizures at 100 mg/kg after administration of the acyclic derivative **13**, but this activity was short acting. The ataxia that had paralleled the activity in most other derivatives was not present, but this advantage could not be exploited because of the lack of potency.

The homopiperazine derivative **14** allows the nitrogens greater conformational flexibility without total freedom of mobility. This compound provided short-acting protection from seizures with no appreciable ataxia but had no advantages over **6**.

Compound **6** showed the most desirable activity/side effect profile seen during these investigations and was selected for a detailed pharmacological investigation.

Compound **6** was tested in all seven phases of the Antiepileptic Drug Discovery (ADD) Program of the NIH–NINCDS.[13] In addition, a number of pharmacological procedures described in the Experimental Section were performed to assess anticonvulsant and side-effect activity.

After single intraperitoneal (ip) doses of 7 mg/kg of **6**, anticonvulsant effects (measured by MES) peaked roughly 30 min after administration and were undetectable 90 min after administration, suggesting rapid drug elimination. ED_{50} values for MES and behavioral side effects of **6** are shown in Table II, with results for phenytoin (5,5-diphenylhydantoin) listed for comparison. Compound **6** protected mice and rats from tonic extensor seizures and was adequately absorbed orally in both species. Mice were judged ataxic by the rotorod procedure only when high doses of **6** were given, but fell from the inverted wire mesh with an ED_{50} of 16 mg/kg ip. This dose is only twice the MES ED_{50} (Table II). In addition, mouse body temperature was reduced (−5 °F) after doses of 30 mg/kg ip, and spontaneous locomotor activity was reduced by roughly 50% after a dose of 40 mg/kg ip. These results indicate that at 4–7 times the MES ED_{50} of **6**, significant depression of central nervous system function and hypothermia occurred. Compound **6** at doses of 15–40 mg/kg ip or 40–100 mg/kg po did not prevent threshold clonic seizures in mice caused by subcutaneous administration of 85 mg/kg pentylenetetrazol. The above profile of pharmacological activity for **6** in rodents is quite similar to that of phenytoin and different from that of phenobarbital, ethosuximide, benzodiazepines, or valproic acid. The major differences between compound **6** and phenytoin were a more rapid apparent elimination of **6** and the appearance of ataxia in some mice given less than 10 mg/kg of **6** (inverted wire mesh test). Such a profile of anticonvulsant activity predicts that **6** would be useful for the treatment of generalized tonic-clonic and partial seizures but not generalized absence seizures.

Experimental Section

All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were

(13) Krall, R. L.; Penry, J. K.; White, B. G.; Kupferberg, H. J.; Swinyard, E. A. *Epilepsia (N.Y.)* **1978**, *19*, 409.

Table II. Calculated Doses for Anticonvulsant Effect or Behavioral Side Effects of Compound 6 and Phenytoin in Rodents

drug	species	time of test, h	route	test	lab	ED_{50}	ED_{10}	ED_{90}
6	mouse	0.5	ip	MES[a]	A[b]	7.5	5.0	11.2
6	mouse	0.5	ip	MES	B[c]	7.5	5.4	10.7
6	mouse	0.5	ip	ROT[d]	A	46	30	69
6	mouse	0.5	ip	SCR[e]	B	16	6.6	39
6	mouse	0.5	po	MES	A	19	10.7	35
6	mouse	1.0	po	MES	B	11.1	7.6	17
6	mouse	1.0	po	ROT	A	139	115	164
6	mouse	0.5	po	SCR	B	35	11	114
phenytoin	mouse	2.0	ip	MES	A	10.4	8.4	13
phenytoin	mouse	2.0	ip	MES	B	7.4	3.7	15
phenytoin	mouse	2.0	ip	ROT	A	71	60	86
phenytoin	mouse	2.0	ip	SCR	B	45	33	63
phenytoin	mouse	2.0	po	MES	A	9.8	NA[f]	NA
phenytoin	mouse	2.0	po	MES	B	8.3	4.9	14
phenytoin	mouse	2.0	po	ROT	A	95	NA	NA
phenytoin	mouse	2.0	po	SCR	B	78	50	125
6	rat	0.5	po	MES	A	36	6.6	195
6	rat	4.0	po	ATAX	A	525	340	830
phenytoin	rat	0.5	po	MES	A	33	NA	NA
phenytoin	rat	4.0	po	ATAX	A	>3000		

[a] MES, maximal electroshock test. [b] A, data from ADD Program (NINCDS). [c] B, data from current study. [d] ROT, rotorod ataxia test. [e] SCR, inverted wire mesh ataxia test. [f] NA, not available.

recorded with a Varian EM-390 NMR spectrometer using Me_4Si as the internal reference standard and deuteriochloroform or Me_2SO-d_6 as solvent. Purity was determined by microanalysis and by TLC with 0.25-mm-thick plates coated with silica gel G as the stationary phase. IR spectra were recorded with a Nicolet XS-20 FT-IR spectrometer using KBr pellets. All compounds possessed microanalytical and spectral data consistent with the proposed structures.

General Synthetic Procedure. For preparation of the side-chain alkoxide, the appropriate alcohol (1.35 mol) was dissolved in toluene under a nitrogen atmosphere. One molar equivalent of sodium metal was introduced and the reaction mixture was gradually warmed and maintained at reflux for 24 h.

The reaction mixture was cooled and 1 molar equiv of 2,6-dichloropyridine was added in one portion. The reaction mixture was heated to reflux and maintained there for 24 h after which time it was cooled, concentrated in vacuo, triturated with petroleum ether, and filtered. The filtrate was purified on a silica gel column with toluene as the eluent to afford the pure 2-alkoxy-6-chloropyridine.

A solution of 2-alkoxy-6-chloropyridine in 1-butanol (0.3 M) was treated with 2 molar equiv of the appropriate amine (R_1R_2NH). The reaction mixture was heated at reflux temperature for 48 h, cooled, and concentrated in vacuo. After dilution with water the product was extracted into ethyl acetate, washed with water, dried, and concentrated in vacuo. A solution of the oil in 2-propanol was treated with 2 molar equiv of HCl dissolved in 2-propanol. This solution was diluted to turbidity with anhydrous ether and was cooled. The resulting crystals were filtered, washed with ether, and dried in vacuo to afford the indicated products.

2-Chloro-6-(2-methylpropoxy)pyridine. 2-Methyl-1-propanol (100 g, 1.35 mol) was dissolved in toluene (1 L) under a nitrogen atmosphere, and the solution was treated portionwise with sodium metal (23 g, 1 mol) during 0.5 h. The reaction mixture was gradually warmed and maintained at reflux temperature for 24 h, cooled, and treated with 2,6-dichloropyridine (148 g, 1 mol) in one portion. The reaction mixture was heated and maintained at reflux temperature for 24 h, after which time it was cooled, concentrated in vacuo, triturated with petroleum ether (1 L), and filtered. The filtrate was concentrated in vacuo to an oil (170 g, 91% crude yield). Purification using flash chromatography with silica gel and toluene as eluent afforded analytically pure material (156 g, 84%). NMR ($CDCl_3$, δ): 7.32 (dd, 1 H, J = 8.0 Hz, Py H-4), 6.67 (d, 1 H, J = 8.0 Hz, Py H-3 or H-5), 6.57 (d, 1 H, J = 8.0 Hz, Py H-3 or H-5), 4.0 (d, 2 H, J = 6.0 Hz, CH_2CH), 2.11 (m, 1 H, CH), 1.1 (d, 6 H, J = 6.5 Hz, $(CH_3)_2CH$). Anal. ($C_9H_{11}ClNO$) C, H, Cl, N.

1-[6-(2-Methylpropoxy)-2-pyridinyl]-4-methylpiperazine Hydrochloride (10). A solution of 2-chloro-6-(2-methylpropoxy)pyridine (18.6 g, 0.1 mol) in 1-butanol (30 mL) was treated with 1-methylpiperazine (20 g, 0.2 mol) and the reaction mixture was heated at reflux temperature for 48 h, cooled, and concentrated in vacuo. After dilution with water (400 mL) the product was extracted into ethyl acetate (150 × 4 mL), washed with water (100 × 3 mL), dried over K_2CO_3, and concentrated in vacuo. The oil (44 g) was dissolved in 2-propanol (100 mL) and treated with a solution of 7.3 g of HCl dissolved in 2-propanol (50 mL). The warmed solution was diluted to turbidity with anhydrous ether and then cooled. The crystals were filtered, washed with ether, and dried in vacuo at 45 °C for 24 h to give the product **10** (49 g, 86%), mp 207-208 °C. NMR (Me_2SO-d_6, δ): 11.05 (br, 1 H, HCl), 7.45 (dd, 1 H, J = 8.0 Hz, Py H-4), 6.40 (d, 1 H, J = 8.0 Hz, Py H-3 or H-5), 6.11 (d, 1 H, J = 8.0 Hz, Py H-3 or H-5), 3.94 (d, 2 H, J = 6.6 Hz, OCH_2CH), 3.58–2.85 (m, 8 H, piperazine), 2.75 (s, 3 H, NCH_3), 1.96 (m, 1 H, CH_2CH), 0.91 (d, 6 H, J = 6.7 Hz). Anal. ($C_{14}H_{23}N_3O$·HCl) C, H, N, Cl.

Pharmacological Methods. The test compounds were dissolved in water or suspended in 0.2% Methocel and evaluated for their ability to prevent the tonic extensor component of maximal seizures induced in male Swiss-Webster mice by electroshock (MES test). The mice ranged in weight from 25 to 32 g and were allowed food and water prior to testing. Doses of the drugs were calculated as the free base.

Drugs were administered intraperitoneally (ip). Five mice were tested at each of three doses (30, 100, 300 mg/kg) and at three time points (0.5, 2, 4 h).

The mice were subjected to a 90-mA, 1-ms, monophasic pulse at 100-Hz current delivered through ear clips for 0.2 s. This current strength was approximately 4 times that required to produce seizures in 99% of mice tested and reliably produces seizures in 100% of control mice. Prevention of tonic hind limb extension was taken as an anticonvulsant effect.

Behavioral side effects were measured in mice by inversion of a square of wire mesh which untreated mice easily clung to but from which impaired mice fell.[14] In addition, spontaneous locomotor activity of mice was measured by an automated procedure.[15] Rats were tested against maximal electroshock[13] and in a subjective assessment of behavioral impairment. Median effective doses were determined by a probit analysis.[16]

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Registry No. 1, 108122-22-1; 1·HCl, 108122-23-2; **2**, 108122-24-3; **3**, 51047-54-2; **3**·HCl, 38500-97-9; **4**, 108122-25-4; 4·HBr, 108122-26-5; **5**, 108122-27-6; **5**·HCl, 108122-28-7; **6**, 108122-29-8; **6**·HCl, 108122-30-1; **7**, 108148-27-2; **7**·xHCl, 108122-31-2; **8**, 108122-32-3; **9**, 108122-33-4; **9**·2HCl, 108122-34-5; **10**, 108122-35-6; **10**·HCl, 108122-36-7; 11, 108148-28-3; **12**, 108122-37-8; **13**, 108122-38-9; **14**, 108122-39-0; **14**·xHCl, 108122-40-3; $CH_3O^-Na^+$, 124-41-4; $CH_2CH_3O^-Na^+$, 141-52-6; $(CH_3)_2CHO^-Na^+$, 683-60-3; $(CH_3)_2CHCH_2O^-Na^+$, 13259-29-5; $(CH_3)_2N(CH_2)_2O^-Na^+$, 37616-36-7; $H_2N(CH_2)_2N(CH_3)_2$, 108-00-9; 2,6-dichloropyridine, 2402-78-0; cyclohexanol sodium salt, 22096-22-6; cyclopropanemethanol sodium salt, 34006-50-3; cyclohexanemethanol sodium salt, 108122-41-4; 2-cyclohexyloxy-6-chloropyridine, 108122-42-5; 2-methoxy-6-chloropyridine, 17228-64-7; 2-ethoxy-6-chloropyridine, 42144-78-5; 2-(1-methylethyloxy)-6-chloropyridine, 89481-98-1; 2-chloro-6-(2-methylpropoxy)pyridine, 108122-43-6; 2-cyclopropylmethoxy-6-chloropyridine, 108122-44-7; 2-cyclohexylmethoxy-6-chloropyridine, 108122-45-8; 2-[(2-dimethylamino)ethyl]-6-chloropyridine, 108122-46-9; piperazine, 110-85-0; *N*-methylpiperazine, 109-01-3; piperidine, 110-89-4; morpholine, 110-91-8; hexahydro-1*H*-1,4-diazepine, 505-66-8.

Synthesis and Anticonvulsant Activity of Analogues of 4-Amino-*N*-(1-phenylethyl)benzamide

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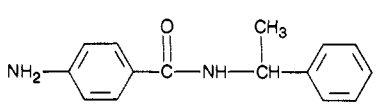
A group of amides and amines related to 4-amino-*N*-(1-phenylethyl)benzamide, 1, were prepared in a study on the relationship of structure to anticonvulsant activity in this compound. Acylation and alkylation of the amino group of 1 resulted in almost total loss of anticonvulsant activity. Insertion of a methylene between the 4-amino group and the aromatic ring of 1 produced a slight increase in anticonvulsant potency and a significant increase in toxicity. Hydride reduction of the amide carbonyl in 1 also yielded compounds having a slightly lower ED50 against convulsions induced by electroshock and a much lower TD50 in the rotorod assay. Modification of the 1-phenylethyl group of 1 also decreased anticonvulsant potency.

A series of prior reports have described the anticonvulsant effects of aminobenzamides of alkyl-, aryl- and arylalkylamines.[1-3] The initial studies on this series of amides have shown the 4-aminobenzamides to be more effective anticonvulsants than the 3-amino derivatives, with the 2-aminobenzamides essentially inactive in most anticonvulsant tests. Maximum anticonvulsant activity in the 4-aminobenzamides is observed in those amides derived from aryl- or arylalkylamines. Recent studies[4] on a series of 4-aminophenylacetamides have shown significant loss of anticonvulsant activity resulting from this insertion of a methylene between the aromatic ring and the amide carbonyl of the aminobenzamides.

The compounds reported in this study were prepared in an investigation of the structure–activity relationships for the anticonvulsant 4-aminobenzamide 1. Racemic 1



1

has been identified in a previous report[1] as an effective anticonvulsant in seizures induced by electroshock and pentylenetetrazole in mice and rats. The preliminary anticonvulsant activity profile for 1 is similar to that for phenobarbital and phenytoin in the same assays. Compound 1 is more effective against electroshock-induced convulsions, ED50 = 18.02 mg/kg, than against pentylenetetrazole-induced seizures, ED50 = 41.72 mg/kg. Rats pretreated orally twice daily for 7 days with 28 mg/kg of 1 showed no significant increase in hexobarbital sleep time. The rotorod toxicity for 1 is TD50 = 170.78 mg/kg while the hypnotic dose (HD50) and lethal dose (LD50) are 461.76 and 718.18 mg/kg, respectively. The molecular modifications of 1 reported in this study include alkylation and acylation of the aromatic amino group, methylene insertion between the amino and aromatic groups to produce compounds of enhanced basicity and conformational degrees of freedom, reduction of the amide carbonyl to yield the corresponding amines, and modifications of the 1-phenylethyl group.

Chemistry

The 4-(alkylamino)- and 4-(acylamino)benzamides prepared in this study are listed in Table I. The monomethyl analogues were prepared by condensation of methyl 4-(*N*-methylamino)benzoate and 1-phenylethylamine in a sealed tube at 180 °C. The methyl 4-(*N*-methylamino)benzoate was prepared by treating the tosylate of 4-aminobenzoic acid with dimethyl sulfate followed by hydrolysis according to the methods of Iwanami et al.[5] Dimethylation of the aromatic amino group was accomplished by treating the primary amine 1 with formaldehyde and sodium cyanoborohydride under acidic conditions via the procedure of Borch et al.[6] Acylation of 1 by reaction with the appropriate acyl chloride under nonaqueous conditions gave compounds **8–10**.

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