absence of fixed concentrations of xanthine by using Schild equation.[35]

Acknowledgment. M.T.S. was supported by a grant from the International Life Sciences Institute (Washington, D.C.). D.U. was on leave from the Pharmakologisches Institut der Universität Heidelberg with support of the Deutsche Forschungsgemeinschaft (Uk 4.1-1).

Registry No. 1, 58-55-9; **2**, 961-45-5; **3**, 85872-58-8; **4**, 80206-91-3; 4·Na, 120362-60-9; **5**, 35873-49-5; **6**, 5438-77-7; **7**, 58-08-2; **8**, 6439-88-9; **9**, 120362-45-0; **10**, 120362-46-1; **11**, 120362-47-2; **12**, 120362-48-3; **13**, 110166-60-4; **14**, 31542-62-8; **15**, 85872-53-3; **16**, 94781-78-9; **17**, 89073-57-4; **18**, 102146-07-6; **19**, 106686-66-2; **20**, 31542-63-9; **21**, 120362-49-4; **22**, 120362-50-7; **23**, 120362-51-8; **24**, 120362-52-9; **25**, 120362-53-0; **26**, 120362-54-1; **27**, 63908-26-9; **28**, 94781-84-7; **29**, 94781-85-8; **30**, 1076-22-8; **31**, 41078-02-8; **32**, 120362-55-2; **33**, 120362-56-3; **34**, 120362-57-4; **35**, 120362-58-5; **36**, 6136-37-4; **37**, 2850-37-5; **38**, 120362-59-6; methyl iodide, 74-88-4; propylurea, 627-06-5; ethyl cyanoacetate, 105-56-6; 1-propyl-6-aminouracil, 53681-47-3; 1-propyl-6-amino-5-nitrosouracil, 120362-61-0; 1-propyl-5,6-diaminouracil, 76194-07-5; benzaldehyde, 100-52-7; 1-propyl-5-(benzylideneamino)-6-aminouracil, 120362-62-1; *p*-carboxybenzaldehyde, 619-66-9; 1-propyl-5-[(*p*-carboxybenzylidene)amino]-6-aminouracil, 120362-63-2; *p*-sulfobenzoic acid, potassium salt, 22959-32-6; 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride, 25952-53-8; cyclohexanecarboxaldehyde, 2043-61-0; 1-propyl-5-(cyclohexylideneamino)-6-aminouracil, 120362-64-3; malonic acid, 141-82-2; methylurea, 598-50-5; 1-methylbarbituric acid, 2565-47-1; 3-methyl-6-chlorouracil, 4318-56-3; benzylamine, 100-46-9; 3-methyl-6-(benzylamino)uracil, 5759-79-5; 3-methyl-5-nitroso-6-(benzylamino)uracil, 5770-20-7; propylurea, 627-06-5; 1-propylbarbituric acid, 5496-93-5; 3-propyl-6-chlorouracil, 50721-48-7; 3-propyl-6-(benzylamino)uracil, 120362-65-4; 3-propyl-5-nitroso-6-(benzylamino)uracil, 120362-66-5.

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

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The anticonvulsant effect of a series of 6-alkyl-*N*,*N*-disubstituted-2-pyridinamines is described. An investigation was carried out to optimize the anticonvulsant activity and reduce behavioral side effects in this series. Three compounds (**7**, **8**, **10**; Table I) were selected from initial screening for a more complete pharmacological evaluation. While each of these compounds was a potent anticonvulsant agent with ED_{50} values from 5 to 10 mg/kg, the activity was accompanied by significant behavioral side effects including decreased spontaneous locomotion, ataxia, and ptosis.

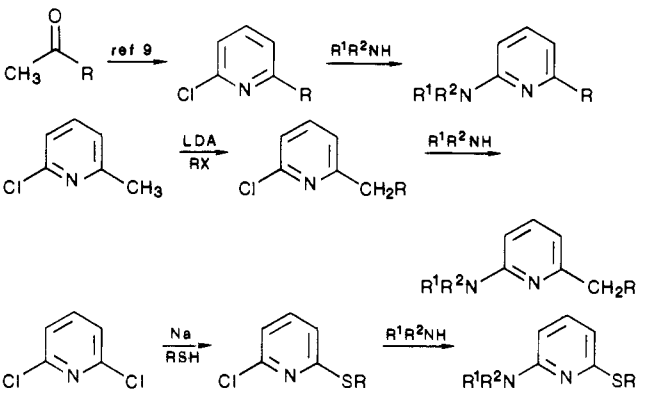
Recently, we have described the anticonvulsant activity of a series of 6-alkoxy-*N*,*N*-disubstituted-2-pyridinamines.[1] The most encouraging results were obtained with 1-[6-(2-methylpropoxy)-2-pyridinyl]piperazine, A (Figure 1). While the potency of A was nearly equal to diphenylhydantoin (phenytoin), a clinically useful anticonvulsant agent, there was insufficient separation between the efficacious dose and the dose causing central nervous system depression and hypothermia. In addition, A possessed a relatively short duration of anticonvulsant activity.

Further investigation of this structural class, in collaboration with the NIH–NINCDS Antiepileptic Drug Discovery Program,[2] revealed the potent anticonvulsant activity of the related 6-alkyl-*N*,*N*-disubstituted-2-pyridinamines, B (Figure 1).

2-Piperazinylpyridine has been reported[3,4] to be useful for the treatment of Parkinson's disease and the 3-, 5-, and 6-substituted 2-piperazinylpyridines have been reported to possess a diverse range of pharmacological properties.[5-7] To our knowledge, 6-alkyl-2-piperazinylpyridines have not been described as possessing anticonvulsant activity.

Initially we observed that 1-(6-hexyl-2-pyridinyl)-piperazine, **7** (Table I), was active against seizures induced by maximal electroshock (MES),[8] a model for generalized tonic–clonic seizures. The anticonvulsant potency of this compound was comparable to that of A but exhibited a greater separation between doses having an anticonvulsant effect and those demonstrating behavioral side effects (ataxia). Because of this encouraging result, we examined a series of 6-alkyl-*N*,*N*-disubstituted-2-pyridinamines in

Scheme I



† Department of Chemistry.
‡ Department of Pharmacology.

(1) Pavia, M. R.; Taylor, C. P.; Hershenson, F. M.; Lobbestael, S. J. *J. Med. Chem.* **1987**, *30*, 1210.
(2) Kupferberg, H. J.; Gladding, G. D.; Swinyard, E. A. In *Antiepileptic Drugs, Handbook of Experimental Pharmacology*; Frey, H.-H., Janz, D. E.; Springer Verlag: Berlin, 1985; Vol. 74, p 341.
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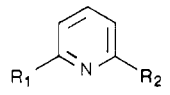
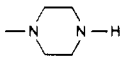
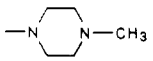
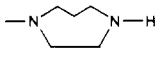
Table I. Structure–Anticonvulsant Activity of 1-(6-Alkyl-2-pyridinyl)piperazines



no.	R_1	R_2	mp, °C	yield,[a] %	molecular formula[b]	minimum effective dose,[c] mg/kg	minimum ataxic dose,[d] mg/kg
1	CH_3		>280	62	$C_{10}H_{15}N_3 \cdot 2HCl$	>300	30
2	$(CH_2)_2CH_3$	*i*	210–213	6	$C_{12}H_{19}N_3 \cdot 3HCl$	10	3
3	$CH(CH_3)_2$	*i*	218–222	9	$C_{12}H_{19}N_3 \cdot 2HCl$	>300	30
4	$(CH_2)_3CH_3$	*i*	88–90	35	$C_{13}H_{21}N_3 \cdot 1.3C_3H_4O_4$	30	10
5	$C(CH_3)_3$	*i*	232–234	10	$C_{13}H_{21}N_3 \cdot 2HCl$	>300	30
6	$(CH_2)_4CH_3$	*i*	100–101	28	$C_{14}H_{23}N_3 \cdot C_3H_4O_4$	10	30
7	$(CH_2)_5CH_3$	*i*	124–126[e]	12	$C_{15}H_{25}N_3$	10	100
8	$(CH_2)_6CH_3$	*i*	95–96	52	$C_{16}H_{27}N_3 \cdot C_3H_4O_4$	10	100
9	$(CH_2)_7CH_3$	*i*	78–81	37	$C_{17}H_{29}N_3 \cdot C_3H_4O_4$	10	30
10	$(CH_2)_8CH_3$	*i*	92–95	20	$C_{18}H_{31}N_3 \cdot C_3H_4O_4$	10	30
11	$(CH_2)_9CH_3$	*i*	94–96	17	$C_{19}H_{33}N_3 \cdot C_3H_4O_4$	30	100
12	$(CH_2)_2C_6H_5$	*i*	114–116	40	$C_{17}H_{21}N_3 \cdot C_3H_4O_4$	>300	100
13	CH_2-c-C_6H_{11}	*i*	208–210	16	$C_{16}H_{25}N_3 \cdot HCl$	100	100
14	$CH[(CH_2)_5CH_3]_2$	*i*	91–94	56	$C_{22}H_{39}N_3 \cdot C_3H_4O_4$	>300	100
15	$S(CH_2)_3CH_3$	*i*	98–100	26	$C_{13}H_{21}N_3S \cdot C_3H_4O_4$	100	100
16	4-$(CH_2)_6CH_3$	*i*	oil[f]	34		30	100
17	$(CH_2)_6CH_3$		*g*	69	$C_{17}H_{29}N_3 \cdot 2HCl \cdot H_2O$	30	300
18	$(CH_2)_6CH_3$		87–88	52	$C_{17}H_{29}N_3 \cdot C_3H_4O_4$	30	100
19	$(CH_2)_6CH_3$		*h*	63	$C_{16}H_{26}N_2O$	300	>300
20	$(CH_2)_6CH_3$		*h*	47	$C_{17}H_{28}N_2$	>300	>300

[a] Isolated yields. [b] Satisfactory analytical data ±0.4% obtained for all compounds; satisfactory halogen analyses for compounds 1 and 15 and satisfactory water analysis (Karl Fischer) for compound 17. [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) during testing 120 min after ip dosing. [d] Lowest dose level (10, 30, 100, 300, >300 mg/kg) at which two or more mice (N = 5) fell off inverted screen during testing 120 min after ip dosing. [e] Boiling point at 0.1 Torr. [f] ^1H NMR ($CDCl_3$): δ 7.92 (d, 1 H, J = 6.3 Hz), 7.15 (s, 1 H), 7.02 (d, 1 H, J = 6.3 Hz), 3.93 (t, 4 H, J = 5.6 Hz), 3.48 (t, 4 H, J = 5.6 Hz), 2.74 (t, 2 H, J = 7.3 Hz), 1.6–0.8 (m, 13 H). [g] Hygroscopic; melting point not determined. [h] Purified by flash column chromatography. [i] Same as above.

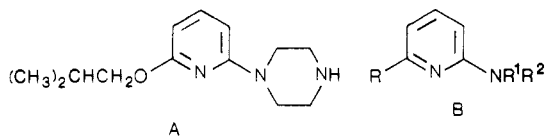


Figure 1.

order to optimize the anticonvulsant/side-effect profile.

Chemistry

The synthetic routes used to prepare the target molecules are illustrated in Scheme I. Target molecules in this series were initially prepared by the method of Mariella.[9] In this route, ethyl formate is condensed with various methyl alkyl ketones in the presence of sodium. Further reaction with cyanoacetamide gives 3-cyano-2-pyridones, which are then hydrolyzed, decarboxylated, and converted into the desired 2-alkyl-6-chloropyridines. Subsequent reaction with an amine results in chlorine displacement to afford the target molecules. This sequence could not be used efficiently for the preparation of analogues required for a structure–activity study because of its length, low yields, and lack of a common advanced intermediate.

An alternate route was devised with commercially available 6-chloro-2-picoline as the starting material. Treatment of this with 1 equiv of cold LDA resulted in abstraction of a proton from the methyl group. Subsequent addition of an alkyl halide to the preformed anion gave the desired 6-chloro-2-alkylpyridines in one operation, generally in high yields. These products were treated with amines to obtain compounds **1–13**, **16–20**. For the preparation of **14**, the intermediate 6-chloro-2-heptylpyridine was alkylated as described above with 1-bromohexane and the product was further reacted with piperazine.

The thio analogue **15** was prepared from 2,6-dichloropyridine by a reaction of butyl mercaptan and sodium metal, this being followed by treatment with piperazine.

Discussion

Compound **7** was found to be a potent anticonvulsant agent against convulsions induced by maximal electroshock (MES). The potency of **7** was comparable to that of other clinically useful antiepileptic agents, but the ratio between the dose of **7** causing ataxia and the anticonvulsant dose (protective index) was only 3. We therefore initiated an investigation in the hope of improving the protective index. The present structure–activity study was based primarily on previous observations with 6-alkoxy-*N*,*N*-disubstituted-2-pyridinamines.[1]

The title compounds can be divided into three structural regions: the pyridine ring, the alkyl side chain, and the N,N-disubstituted group. We initially chose to retain the

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(8) 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.
(9) Mariella, R. P.; Stansfield, R. J. *J. Am. Chem. Soc.* **1951**, *73*, 1368.

Table II. ED_{50} Values (mg/kg ip) in Pharmacological Tests with Compounds 7, 8, 10, and Phenytoin Given to Mice[a]

compound	ED_{50} MES	ED_{50} clonic pentylenetetrazol	ED_{50} ataxia	protective index (ED_{50} ataxia/ED_{50} MES)	ED_{50} locomotion inhibition
7	7.3 (1)		22 (0.5)	3.0	20
7[b]	16.0 (1)	>100 (1)	46 (0.5)	2.9	
8	8.8 (1)		45 (1.5)	5.1	13
8[b]	6.4 (2)	21 (2)	29 (0.25)	4.5	
10	5.6 (4)		30 (1.5)	5.4	26
10[b]	7.8 (6)	>100 (6)	42 (1)	5.4	
phenytoin	8.0 (1.5)		82 (4)	10.3	>65
phenytoin[b]	9.5 (2)	>100 (2)	65 (2)	6.8	
carbamazepine	9.8 (0.25)	>100 (0.25)	41 (0.5)	4.2	50
carbamazepine[b]	8.8 (0.25)	>100 (0.25)	72 (0.25)	8.2	

[a] Value in parentheses is delay between drug administration and pharmacological testing in hours (approximate time of peak drug effect). [b] Data from NINCDS Antiepileptic Drug Discovery Project.

pyridine nucleus and vary the substituents at the 2- and 6-positions of the ring.

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

Small alkyl or small branched-chain alkyl groups attached to the pyridine nucleus (methyl, 1; isopropyl, 3; *tert*-butyl, 5) provided compounds that were devoid of anticonvulsant activity at the doses tested. Severe side effects were observed at 100 mg/kg, including the death of several animals.

Anticonvulsant activity began to appear with the straight-chain alkyl analogues 2 and 4. While activity was seen at doses of 10 and 30 mg/kg, respectively, associated behavioral side effects were observed at doses lower than those demonstrating protection against seizures.

The desired anticonvulsant/side effect profile emerged with the *n*-pentyl analogue 6. Seizure protection was seen at 10 mg/kg and ataxia was not observed until 30 mg/kg. Both effects were short-lasting, with no effects seen 4 h after ip administration of 30 mg/kg. Compound 7 exhibited a clean separation between the desired anticonvulsant efficacy (seen after 10 mg/kg) and ataxia (seen after 100 mg/kg) ip. Other side effects that included excessive urination, salivation, and loss of righting were seen after ip administration of 100 mg/kg. The protective index for 7 was approximately 3 (Table II).

Since a better profile was obtained by increasing the length of the alkyl chain attached to the 6-position of the pyridine ring, we prepared the 7–10 carbon straight-chain analogues (compounds 8–11). All four of these compounds had anticonvulsant activity at low doses (10–30 mg/kg). Beginning with the octyl-containing analogue 9, we observed a delay in the onset of anticonvulsant effects. All of the compounds tested previously caused anticonvulsant effects within 30 min of dosing ip. However, with compounds 9–11, the first observable actions occurred 2 h after ip administration. Four hours after a 30 mg/kg dose, compounds 9–11 protected all test animals from seizures. The delay in onset of pharmacological activity likely is due to the increasing lipophilicity as the length of the alkyl chain increases. While the log *P* for 7[10a] is 2.5, it can be estimated that the corresponding values for 10 and 11 would be ≥4.[10b]

Since the most potent anticonvulsant activity was seen with the C_6–C_9 chain lengths, we prepared the phenethyl and methylenecyclohexyl derivatives 12 and 13. Interestingly, 12 exhibited no anticonvulsant activity up to the highest dose administered (300 mg/kg). More surprisingly, 13 was 10-fold less active than the corresponding acyclic analogues, which indicated that a conformationally mobile *n*-alkyl chain is important for activity. The log *P* for both 7 and 13 were nearly identical (2.5 vs 2.41) and cannot explain the difference in activities observed.

The sulfur analogue of 6 (15) was much less active than 6, confirming the need for a straight-chain alkyl group.

The positional requirement of the alkyl group was explored by study of the 4-substituted analogue 16. Anticonvulsant activity was observed in all test animals given 30 mg/kg, but no protection was seen at 10 mg/kg, indicating a steep dose–response relationship.

Because optimal profiles were seen with 7 and 8, we turned our attention to modifications of the piperazine ring. Methylation of the terminal nitrogen of the piperazine ring afforded 17, which showed a 3-fold decrease in potency, as compared to 7. Loss of activity was also observed when the ring was enlarged as in the homopiperazine analogue 18.

The need for the terminal nitrogen in the group attached to the 6-position of the pyridine was demonstrated with the morpholine analogue 19 and the piperidine analogue 20. Both of these congeners showed a 30-fold decrease in potency as compared to 7.

It can be concluded that an *n*-alkyl group attached to the 2-position and a piperazine attached to the 6-position of a pyridine nucleus afford potent anticonvulsants with good separation between the effective and ataxic doses. Compounds 7, 8, and 10 were chosen for more extensive pharmacological evaluation.

Compounds 7, 8, and 10 prevented maximal electroshock seizures in mice after intraperitoneal administration. The percentage of mice protected against maximal electroshock-induced seizures was related to the administered dose. ED_{50} values for these compounds varied from 5 to 10 mg/kg ip and are shown in Table II with dose–response curves shown in Figure 2.

The time courses of the anticonvulsant actions of compounds 7, 8, and 10 after ip administration are shown in Figure 3. Compound 7 had a rapid onset of anticonvulsant action after 20 mg/kg ip, with protection against maximal electroshock-induced seizures for 2–4 h. Compound 8 had a slower onset of anticonvulsant action (peak effect 4 h after 8 mg/kg ip) that is consistent with slow absorption from the site of administration. These results were confirmed by independent observations of investigators of the NINCDS Antiepileptic Drug Discovery Program (Table II).

Only compound 8 protected more than 50% of the mice from clonic pentylenetetrazol-induced seizures (ED_{50} = 21 mg/kg ip, 2 h after dosing). Compound 10 protected 40%

(10) (a) Nabum, A.; Horvath, C. *J. Chromatogr.* **1980**, *192*, 315. (b) Haky, J.; Young, A. M. *J. Liquid Chromatogr.* **1984**, *7*, 675.

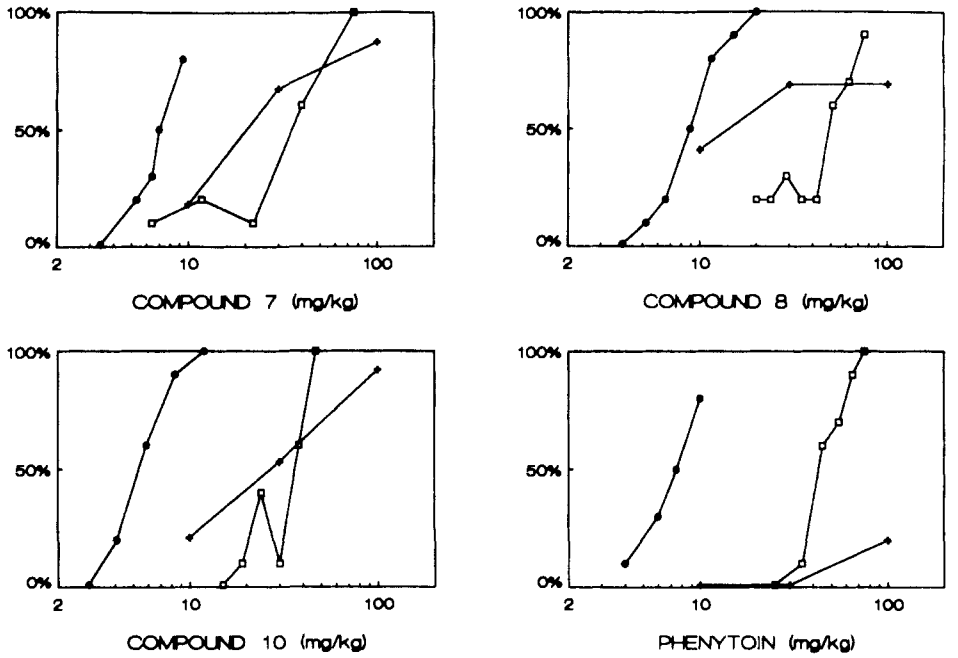

Figure 2. Dose–response relationships for blockade of maximal electroshock seizures (filled circles), inhibition of spontaneous locomotor activity (crosses), and inverted screen ataxia (squares) for compounds **7**, **8**, **10**, and phenytoin given ip to mice. Note that all four compounds prevent maximal electroshock seizures at similar doses but compounds **7**, **8**, and **10** inhibit spontaneous locomotor activity. *Y* axis denotes the percent of mice with anticonvulsant or ataxic actions (N = 10) or the mean percent inhibition of locomotion (N = 14).

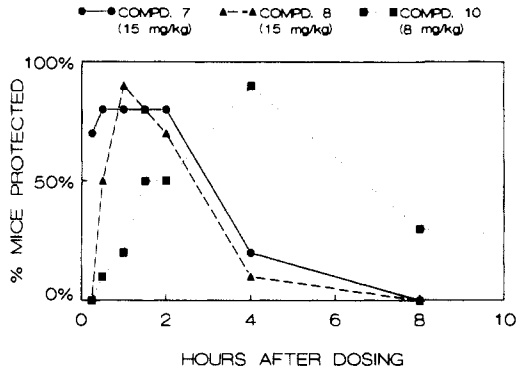

Figure 3. Time course of anticonvulsant action of experimental compounds following a single ip dose to mice. Note increasing delay in anticonvulsant effect with compounds **7**, **8**, and **10**. N = 10 mice per point.

of the mice or less from clonic pentylenetetrazol seizures at doses between 18 and 75 mg/kg ip. Compound **7** did not prevent clonic pentylenetetrazol seizures with doses between 15 and 100 mg/kg ip.

All three compounds caused behavioral side effects in a dose-related manner (Figure 2). Like phenytoin and carbamazepine, each compound caused dose-related ataxia (inverted screen test) with ED_{50} values 3–6 times higher than the ED_{50} for prevention of maximal electroshock seizures. However, in contrast to phenytoin or carbamazepine, all three of the experimental compounds caused inhibition of spontaneous locomotion at doses similar to or below the ED_{50} for ataxia (Table II, Figure 2). In addition, two of 13 mice given 30 mg/kg of compound **7** ip died within 1.5 h and 11 of 12 died after 100 mg/kg within 1.5 h.

Compounds **7**, **8**, and **10** were tested for prevention of focal afterdischarge recorded with wire electrodes in the hippocampus of unanesthetized rats. In this model of partial seizures (see the Experimental Section), phenytoin and carbamazepine prevented afterdischarge from electrical stimulation. This effect occurred in a dose-related manner with no ataxia observed until higher doses were administered. However, compounds **7** and **10** prevented afterdischarge in only a fraction of the rats at doses below the ED_{50} for ataxia. Compound **8** prevented afterdischarge in most rats at doses less than those causing ataxia, but was less effective with high intensity stimuli. These results with compound **8** are similar to those for phenytoin, which prevented afterdischarge to either low or higher intensity stimuli in a dose-related manner and at doses that did not produce ataxia (Figure 4).

It was concluded that the most potent of the (alkylpiperazinyl)pyridines produced anticonvulsant effects but only at doses that also produced significant behavioral side effects of decreased spontaneous locomotion, ataxia, and ptosis.

Experimental Section

All melting points were obtained on a Thomas-Hoover capillary melting point apparatus and are uncorrected. NMR spectra were recorded with a Varian EM-390 NMR spectrometer using TMS as the internal reference standard and deuteriochloroform or DMSO-d_6 as solvents. Purity was determined by microanalysis and by TLC using 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 A. The 2-alkyl-6-chloropyridines were prepared by the method of Mariella and Stansfield.[9]

The halopyridine (0.1 mol) dissolved in 1-butanol (0.5 M) was treated with 2 molar equiv of the appropriate amine. 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 ether, and the organic phase was washed with water, dried, and concentrated in vacuo. Flash column purification or distillation afforded pure amines. A solution of the oil in 2-propanol was treated with 2 molar equiv of HCl dissolved in 2-propanol and diluted to turbidity with ether, or alternatively a solution of the oil in ether was treated with 1 molar equiv of malonic acid dissolved in ether. The resulting crystals were filtered, washed with ether, and dried in vacuo to afford the indicated products.

General Synthetic Procedure B. One equivalent of LDA [prepared at −20 °C in anhydrous THF under nitrogen from the

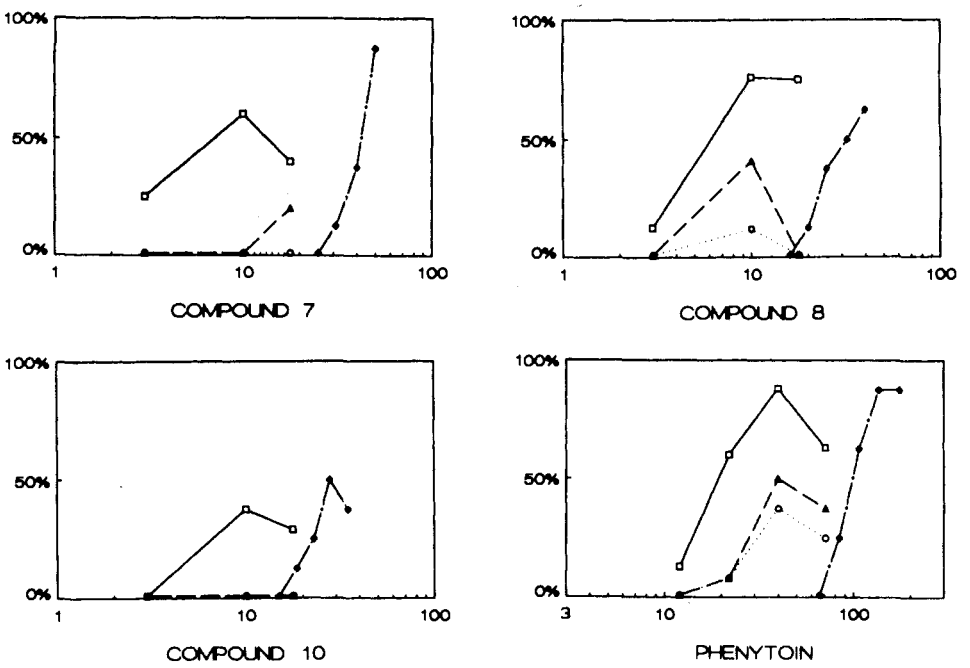

Figure 4. Dose–response relationships for prevention of afterdischarge (focal seizure) in kindled rats by experimental compounds and phenytoin. *Y* axis denotes percentage of rats protected from afterdischarges with electrical stimulation twice (squares), 6 times (triangles), or 8 times (circles) the threshold for afterdischarge before drug treatment. Doses are mg/kg ip. Note that compounds **7**, **8**, and **10** were less effective than phenytoin or carbamazepine against high intensity (6 and 8 times threshold) stimulation. Filled diamonds denote percentage of rats that were ataxic (N = 8 per dose).

treatment of diisopropylamine (1 equiv) with dropwise addition of *n*-BuLi (1 equiv) in hexanes] in anhydrous THF under nitrogen was cooled to −78 °C and treated dropwise with stirring with 6-chloro-2-picoline (1 equiv) dissolved in anhydrous THF (4 M). The mixture was stirred for 1 h at −20 °C and then treated dropwise with the appropriate alkyl halide (1 equiv). The resultant mixture was stirred and gradually warmed to room temperature over a 10-h period. Stirring was continued for an additional 10-h period after which time the reaction mixture was concentrated in vacuo and triturated with petroleum ether. The insoluble materials were filtered off, and the filtrate was concentrated in vacuo to an oil. The oil was applied to a flash column and eluted with ether/petroleum ether (5:95). Fractions containing product were combined and concentrated in vacuo to give the product.

Treatment of the intermediate alkylchloropyridine with the substituted amines was carried out as in General Synthetic Procedure A.

General Synthetic Procedure C. The 2-chloro-6-thioalkoxypyridine was prepared by the method Pavia[1] used to prepare the 2-chloro-6-alkoxypyridines.

2-Chloro-6-hexylpyridine. 2-Octanone (256.4 g, 2 mol), ethyl formate (148 g, 2 mol), and sodium (46 g, 2 mol) in ether provided, by the method of Mariella and Stansfield,[9] 76 g of 2-chloro-6-*n*-hexylpyridine (bp 130–132 °C/15 torr).

1-(6-Hexyl-2-pyridinyl)piperazine (7). A solution of 2-chloro-6-hexylpyridine (19.8 g, 0.1 mol) in 1-butanol (200 mL) was treated with piperazine (17.2 g, 0.2 mol), and the reaction mixture was heated at reflux temperature for 48 h and concentrated in vacuo. After dilution with water (300 mL), the product was extracted into ether (2 × 100 mL), and the ether phase was washed with water (3 × 50 mL), dried over K_2CO_3, and concentrated in vacuo. The oil was distilled (bp 124–126 °C/0.1 torr) to give 15.8 g (63%) of product **7**.

2-Chloro-6-nonylpyridine. To a solution of diisopropylamine (5.5 mL, 0.04 mol) in anhydrous THF (50 mL) at −20 °C under nitrogen was added dropwise with stirring nBuLi (2.186 M in hexanes, 18 mL) over a period of 5 min. The mixture was then cooled to −78 °C, and 6-chloro-2-picoline (5 g, 0.039 mol) in anhydrous THF (10 mL) was added dropwise. The mixture was stirred at −78 °C for 1 h and was then treated dropwise with 1-bromooctane (7.7 g, 0.04 mol). The mixture was stirred and allowed to warm to room temperature over a 10-h period. Stirring was continued for 10 h longer. The mixture was concentrated in vacuo and the residue was triturated with petroleum ether (100 mL). The insoluble materials were filtered off, and the filtrate was concentrated in vacuo to an oil. Purification by flash column chromatography [ether/petroleum ether (5:95) as eluent] afforded analytically pure material (4.2 g, 45%).

1-(6-Nonyl-2-pyridinyl)piperazine Monomalonate (10). A solution of 2-chloro-6-*n*-nonylpyridine (3.5 g, 14.6 mmol) in 1-butanol (30 mL) was treated with piperazine (2.5 g, 29.2 mmol) and the reaction mixture was heated at reflux temperature for 48 h and concentrated in vacuo. After dilution with water (30 mL), the product was extracted into ether (2 × 10 mL), the organic layer washed with water (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The oil (2.1 g) was dissolved in ether (10 mL) and treated with a solution of malonic acid (0.75 g, 7.3 mmol) in ether (25 mL). The precipitate was filtered off, washed with ether, and dried in vacuo to give 2.3 g of product (47%), mp 92–95 °C.

2-(Butylthio)-6-chloropyridine. *n*-Butyl mercaptan (9.9 g, 0.109 mol) was dissolved in toluene (250 mL) under a nitrogen atmosphere, and the solution was treated portionwise with sodium metal (2.5 g, 0.109 mol) during 15 min. The reaction mixture was gradually warmed and maintained at reflux temperature for 4 h, cooled, and treated with 2,6-dichloropyridine (14.8 g, 0.1 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 (500 mL), and filtered. The filtrate was concentrated in vacuo to an oil. Purification by flash chromatography with silica gel and CH_2Cl_2/petroleum ether (1:9) as eluent afforded analytically pure material (13.1 g, 65%).

1-[6-(Butylthio)-2-pyridinyl]piperazine Monomalonate (15). A solution of 2-(butylthio)-6-chloropyridine (2 g, 10 mmol) in 1-butanol (10 mL) was treated with piperazine (1.7 g, 20 mmol) and the reaction mixture was heated at reflux temperature for 8 h, cooled, and concentrated in vacuo. After dilution with petroleum ether (40 mL), the insolubles were filtered off, and the filtrate was concentrated in vacuo to an oil. Purification by flash column chromatography with silica gel and CH_2Cl_2 as eluent afforded analytically pure material (1 g, 50%).

The oil was dissolved in ether (10 mL) and treated with a solution of malonic acid (0.4 g, 3.8 mmol) in ether (20 mL). The precipitate was filtered, washed with ether, and dried in vacuo to give 1.2 g of product, mp 98–100 °C (80%).

Pharmacological Methods. Drug Preparation. For pharmacological procedures, drugs were finely pulverized with mortar and pestle, suspended in 0.2% (carboxymethyl)cellulose

and 0.9% NaCl, and injected ip or po (gavage) in a volume of 10 mL/kg (mice) or 5 mL/kg (rats). In testing performed by NINCDS, drugs were suspended or dissolved in 30% polyethylene glycol and injected in a volume of 10 mL/kg (mice) or 4 mL/kg (rats).

Animals. Male Swiss-Webster mice (22–32 g, Buckberg Labs, Tomkin Cove, NY, or Charles River, Portage, MI) were used for electroshock and ataxia experiments; male CF-1 mice (25–35 g, Charles River, Portage, MI, or Wilmington, MA) were used for threshold clonic seizures from pentylenetetrazol and for all testing from NINCDS. Male Sprague–Dawley rats (125–150 g, Charles River, Portage MI) were used for ataxia experiments, and somewhat larger rats (270–300 g) were used for implantation of hippocampal electrodes. All rodents were allowed free access to food and water prior to testing.

Maximal Electroshock. For mice, shocks were applied through earclip electrodes from a Ugo Basile (Milan, Italy) electroshock apparatus; 90-mA monophasic pulses of 1-ms duration, 100 Hz for 0.2 s. This stimulus intensity was approximately 4 times the threshold for tonic extensor seizures. In tests at the NINCDS, shocks were applied through corneal electrodes from a Wahlquist (Salt Lake City, UT) electroshock apparatus, 50-mA (zero to peak) sinusoidal current, 60 Hz for 0.2 s. In both cases, an anticonvulsant effect was scored if tonic extensor seizures (extension of the hindlimbs parallel to the body) were prevented.

Pentylenetetrazol Threshold Seizures. Pentylenetetrazol was dissolved in 0.9% NaCl and administered subcutaneously (10 mL/kg) at the dorsal part of the neck (85 mg/kg). Mice were observed for 30 min following injection. Prevention of all clonic seizures (≥5 s of forelimb clonus) was scored as an anticonvulsant effect.

Afterdischarge in Kindled Rats. Rats were anesthetized and stereotaxically implanted with paired wire electrodes in the dorsal hippocampus of the brain. At least 1 week after surgery, electrical stimuli were delivered to the implanted electrodes at 30-min intervals for a total of 8 h (biphasic pulses, 1 ms each phase, 500 μA peak-to-peak, 10 Hz for 10 s). Such intermittent stimulation was given for 8-h periods on each of four alternating days. At least 3 days later, rats were used for pharmacological testing. Each rat was tested for the threshold electrical stimulus to produce a focal seizure (afterdischarge). Beginning with a peak-to-peak stimulus of 40 μA (biphasic pulses, 1 ms each phase, 60 Hz for 1 s), the stimulus was incremented by 20% at intervals of 1 min until a focal afterdischarge (rapidly repeated high-voltage EEG spikes lasting for at least 3 s) occurred. The stimulus intensity that first caused an afterdischarge was taken as the untreated afterdischarge threshold. Following drug administration, each rat received an electrical stimulus at twice the mean untreated threshold. If no afterdischarge occurred, additional stimuli were given at 4, 6, and 8 times the untreated threshold until an afterdischarge was recorded.

Anticonvulsant effects were scored separately for each of the stimulus intensities (2, 4, 6, or 8 times the untreated threshold).

Measurement of Ataxia. Ataxia in mice is defined as the lowest dose level at which two or more animals ($N = 5$) fell from an inverted wire mesh screen[11] or, in NINCDS studies, from a rotating rod.[12] In rats, ataxia was evaluated by scoring uncoordinated locomotion on a flat surface (uneven gait in each of three trials) and by delayed righting responses (righting more than 1 s after being placed supine in each of three trials).

ED_{50} Determinations. Doses of drug causing 50% of the maximal effect were determined by quantal probit analysis for anticonvulsant and ataxia measurements.[13] For inhibition of spontaneous locomotion, ED_{50} was estimated graphically from log dose–response curves.

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Registry No. 1, 55745-89-6; 1·2HCl, 120144-91-4; **2**, 120145-32-6; **2**·3HCl, 120144-92-5; **3**, 120145-33-7; **3**·2HCl, 120144-93-6; **4**, 120144-94-7; **4**·$C_3H_4O_4$, 120144-95-8; **5**, 120145-34-8; **5**·2HCl, 120144-96-9; **6**, 120144-97-0; **6**·$C_3H_4O_4$, 120144-98-1; **7**, 120144-99-2; **8**, 120145-00-8; **8**·$C_3H_4O_4$, 120145-01-9; **9**, 120145-02-0; **9**·$C_3H_4O_4$, 120145-03-1; **10**, 120145-04-2; **10**·$C_3H_4O_4$, 120145-05-3; **11**, 120145-06-4; **11**·$C_3H_4O_4$, 120145-07-5; **12**, 120145-08-6; **12**·$C_3H_4O_4$, 120145-09-7; **13**, 120145-35-9; **13**·HCl, 120145-10-0; **14**, 120145-11-1; **14**·$C_3H_4O_4$, 120145-12-2; **15**, 120145-13-3; **15**·$C_3H_4O_4$, 120145-14-4; **16**, 120145-15-5; **17**, 120145-36-0; **17**·2HCl, 120145-16-6; **18**, 120145-17-7; **18**·$C_3H_4O_4$, 120145-18-8; **19**, 120145-19-9; **20**, 120145-20-2; $Br(CH_2)_2CH_3$, 106-94-5; $Br(CH_2)_3CH_3$, 109-65-9; $Br(CH_2)_4CH_3$, 110-53-2; $Br(CH_2)_6CH_3$, 629-04-9; $Br(CH_2)_7CH_3$, 111-83-1; $Br(CH_2)_9CH_3$, 112-29-8; cyanoacetamide, 107-91-5; 6-chloro-2-heptylpyridine, 120145-24-6; 1-bromohexane, 111-25-1; *N*-methylpiperazine, 109-01-3; homopiperazine, 505-66-8; morpholine, 110-91-8; piperidine, 110-89-4; 2-chloro-6-hexylpyridine, 109201-48-1; 2-octanone, 111-13-7; ethyl formate, 109-94-4; piperazine, 110-85-0; 2-chloro-6-nonylpyridine, 120145-26-8; 6-chloro-2-picoline, 18368-63-3; *n*-butylmercaptan, 109-79-5; 2-(butylthio)-6-chloropyridine, 87512-14-9; 2,6-dichloropyridine, 2402-78-0; 2-chloro-6-propylpyridine, 120145-21-3; 2-chloro-6-isopropylpyridine, 120145-22-4; 2-chloro-6-butylpyridine, 40273-58-3; 2-chloro-6-*tert*-butylpyridine, 97691-23-1; 2-chloro-6-pentylpyridine, 120145-23-5; 2-chloro-6-octylpyridine, 120145-25-7; 6-chloro-2-decylpyridine, 120145-27-9; 2-chloro-6-(2-phenylethyl)pyridine, 120145-28-0; 2-chloro-6-(cyclohexylmethyl)pyridine, 120145-29-1; 2-chloro-6-(tridecan-7-yl)pyridine, 120145-30-4; 2-chloro-4-heptylpyridine, 120145-31-5; (2-bromoethyl)benzene, 103-63-9.

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Phencyclidine-like Effects of Tetrahydroisoquinolines and Related Compounds

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A series of 1,2,3,4-tetrahydroisoquinolines, tetrahydrothieno[2,3-*c*]pyridines, and related compounds were evaluated for their ability to inhibit binding of [^{3}H]-1-[1-(2-thienyl)piperidine and [^{3}H]-*N*-allylnormetazocine to phencyclidine (PCP) and σ receptors, respectively. A representative series of compounds was evaluated in behavioral assays to determine the ability of the compounds to induce PCP-like stereotyped behavior and ataxia. All of the compounds caused stereotyped behavior and ataxia, indicating their agonist actions at the PCP site.

Phencyclidine (PCP) was originally developed as a general anesthetic agent,[1] which was withdrawn from human use because of unwanted side effects, often resembling acute schizophrenia.[2] These observed side effects, how-

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