6.0 mg/kg of DSCG was given intraperitoneally at intervals ranging from 5 to 120 min prior to challenge.

Acknowledgment. We thank Dr. C. Rehm and his staff in the Department of Analytical Chemistry for the analyses.

Registry No. **2a**, 97000-05-0; **2b**, 85064-08-0; **2c**, 97000-06-1; **2d**, 97000-07-2; **2e**, 97000-08-3; **2f**, 97000-09-4; **2g**, 97000-10-7; **2h**, 97000-11-8; **2j**, 97000-12-9; **4a**, 86048-40-0; **4b**, 88362-76-9; **4c**, 88362-77-0; **4c** (ammonium salt), 97000-19-6; **4d**, 97000-14-1; **4e**, 88362-75-8; **4f**, 97000-15-2; **4g**, 97000-16-3; **4h**, 97000-17-4; **4i**, 97000-18-5; **5a**, 18472-06-5; **5b**, 18471-93-7; $ClCO_2C_2H_5$, 541-41-3; *trans*-$ClCOCH{=}CHC_6H_5$, 17082-09-6; $ClCON(CH_3)_2$, 79-44-7; $(CH_3O)_3CCO_2CH_3$, 18370-95-1; $(C_2H_5O)_3CCO_2C_2H_5$, 57267-03-5; $(C_2H_5O)_3CCH_2CO_2C_2H_5$, 32650-62-7; $(C_2H_5O)_3CH$, 122-51-0; $(C_2H_5O)_3CCH_3$, 78-39-7; $C_6H_5C{=}NH(OC_2H_5)\cdot HCl$, 5333-86-8; $Cl_3CC{=}NH(OCH_3)$, 2533-69-9; 5-chloro-8-hydroxyquinoline, 130-16-5; 5-chloro-7-nitro-8-hydroxyquinoline, 18472-03-2.

Anticonvulsant Activity of Some 4-Aminobenzanilides

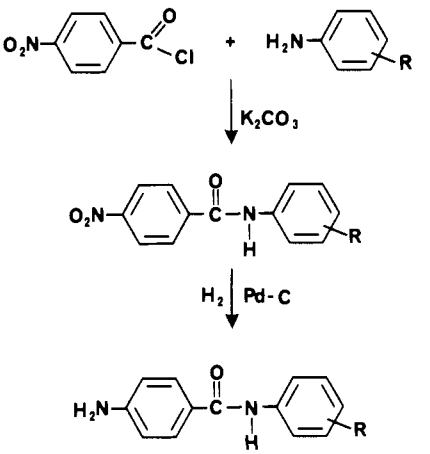
C. Randall Clark,* Ricky T. Sansom, Ching-Ming Lin, and George N. Norris

Division of Medicinal Chemistry, Department of Pharmacal Sciences, School of Pharmacy, Auburn University, Auburn, Alabama 36849. *Received December 3, 1984*

A series of 4-aminobenzanilides derived from ring-alkylated anilines were prepared and evaluated for anticonvulsant activity. These benzanilides were prepared in the course of studies designed to determine the relationship between the benzamide structure and anticonvulsant effects. The compounds were tested in mice against seizures induced by electroshock and metrazole (pentylenetetrazole) and in the rotorod assay for neurologic deficit. All of the 4-aminobenzanilides showed activity at doses of 300 mg/kg against maximal electroshock seizures (MES). The 4-aminobenzanilide derived from 2,6-dimethylaniline (**8**) was the most potent anti-MES compound with an ED_{50} of 2.60 mg/kg and a protective index of 5.77 (PI = TD_{50}/ED_{50}). The activity profile for **8** compares quite favorably with that for phenobarbital and phenytoin in the same assays.

Recent studies in this laboratory[1] have demonstrated significant anticonvulsant potential for the 4-aminobenzamides of some simple dialkyl- and arylalkylamines. Structurally, some of the simplest compounds possessing anticonvulsant properties are the carboxylic acids and their amides.[2] Valproic acid is perhaps the best known example of this class of compounds.[3] The amide of valproic acid has been shown[4] to be as effective as the acid at half the dose. Various reports,[5,6] have described the anticonvulsant effects of substituted cinnamamides. Balsamo et al.[7,8] have described the anticonvulsant and other CNS effects of the *E* and *Z* isomers of some *N*-alkylcinnamamides. Cinromide, 3-bromo-*N*-ethylcinnamamide, has been evaluated as a broad-spectrum anticonvulsant and has a reported anti-MES ED_{50} of 60 mg/kg when administered ip in mice.[6] Several derivatives of 3-phenyl-2-piperidinone have been shown to possess anti-MES and anti-scMet activity in animal models.[9] Amides of substituted benzoic acids[2] including some aminohalobenzamides[10] have also been reported to possess anticonvulsant activity. The local anesthetic amide lidocaine has been shown to suppress the electroencephalogenic manifestations of epileptic seizures in cats.[11]

Scheme I



The unique behavioral profile produced in animals by substituted benzamide neuroleptics such as metoclopramide has generated a considerable amount of interest in recent years.[12] The benzamide neuroleptics are useful in the treatment of schizophrenia and appear to exert their neuroleptic action selectively at a subpopulation of the D-2 type dopamine receptors.[13] These antidopaminergic benzamides differ in some clinical and pharmacological respects from other neuroleptic drugs. In a comparative study with classical neuroleptics these benzamides were generally 1000 times more potent in stimulating rat prolactin secretion than would have been predicted from their potencies in displacing [^{3}H]spiperone from bovine anterior pituitary membranes.[14] The simple 4-aminobenzanilides reported in this paper represent a continuation of our studies on the relationship between benzamide structure

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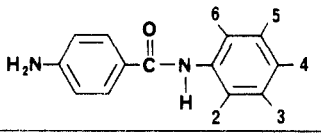
Table I. Physical Properties of 4-Aminobenzanilides[a]



compd	substituent posn 2	3	4	5	6	mp, °C	carbonyl wavenumbers, cm^{-1}	formula	anal.
1	H	H	H	H	H	138–140	1660, 1620	$C_{13}H_{12}N_2O$	C, H, N
2	CH_3	H	H	H	H	152–154	1660, 1620	$C_{14}H_{14}N_2O$	C, H, N
3	H	CH_3	H	H	H	114–116	1660, 1620	$C_{14}H_{14}N_2O$	C, H, N
4	H	H	CH_3	H	H	166–168	1660, 1620	$C_{14}H_{14}N_2O$	C, H, N
5	CH_3	CH_3	H	H	H	165–167	1660, 1620	$C_{15}H_{16}N_2O$	C, H, N
6	CH_3	H	CH_3	H	H	188–191	1660, 1620	$C_{15}H_{16}N_2O$	C, H, N
7	CH_3	H	H	CH_3	H	190–192	1660, 1620	$C_{15}H_{16}N_2O$	C, H, N
8	CH_3	H	H	H	CH_3	212–215	1655, 1620	$C_{15}H_{16}N_2O$	C, H, N
9	H	CH_3	CH_3	H	H	120–122	1660, 1620	$C_{15}H_{16}N_2O$	C, H, N
10	H	CH_3	H	CH_3	H	142–145	1660, 1620	$C_{15}H_{16}N_2O$	C, H, N
11	$CH(CH_3)_2$	H	H	H	H	174–176	1660, 1620	$C_{16}H_{18}N_2O$	C, H, N
12	$CH(CH_3)_2$	H	H	H	CH_3	205–208	1655, 1620	$C_{17}H_{20}N_2O$	C, H, N
13	$CH(CH_3)_2$	H	H	H	CH_2CH_3	189–191	1660, 1620	$C_{18}H_{22}N_2O$	H; C, N[b]

[a] The infrared and nuclear magnetic resonance (^1H) spectra were consistent with structural assignments. [b] Calcd: C, 76.56; N, 9.92. Found: C, 77.48; N, 9.46.

Table II. Anticonvulsant Activity of 4-Aminobenzanilides

compd	MES[a] 30 min	MES[a] 4 h	scMet[a] 30 min	scMet[a] 4 h	toxicity[a,b] 30 min	toxicity[a,b] 4 h
1	++++	++	+++	–	+++	++
2	++++	+++	*c*	*c*	++++[d]	++
3	+++	++	++	–	++	+
4	+++	+++	++++	–	+++	+
5	++++	++	+++	*c*	+++[e]	*e*
6	++	+	+	–	+	–
7	++	–	++	–	–	–
8	++++	++++	*c*	*c*	++++	+++
9	+++	+++	++	++	+++	+
10	++	+	–	–	–	–
11	+++	+	+	–	+	–
12	++++	++	–	–	–	–
13	++++	+++	++	–	++++[e]	+++

[a] ++++, +++, ++, and + signify activity at 30, 100, 300, and 600 mg/kg, respectively; – denotes no activity observed at 600 mg/kg. [b] Determined by the rotorod test. [c] No activity at 300 mg/kg. [d] Loss of righting reflex at 100 mg/kg; LD_{50} less than 600 mg/kg. [e] Loss of righting reflex at 300 mg/kg; LD_{50} less than 600 mg/kg.

and anticonvulsant activity. These compounds are shown to be potent anti-MES agents and further demonstrate the significant anticonvulsant potential associated with this class of compounds.

Results and Discussion

A series of 4-aminobenzanilides were prepared according to well-known synthetic procedures (Scheme I). The intermediate 4-nitrobenzanilides were obtained from 4-nitrobenzoyl chloride and the appropriate alkylaniline under Schotten–Baumann type[15] conditions. The resulting 4-nitrobenzanilides were crystalline solids, showing carbonyl absorption in the infrared spectrum at approximately 1675 cm^{-1}. The aromatic nitro group was reduced by low-pressure catalytic hydrogenation, and the physical properties of the resulting 4-aminobenzanilides are reported in Table I.

The results of the initial anticonvulsant and toxicity evaluation of the 4-aminobenzanilides are reported in Table II. The preliminary screening was done at doses of the test compounds from 30 up to 600 mg/kg administered ip in mice and evaluated against maximal electroshock seizures (MES) and subcutaneous metrazole (scMet) induced convulsions and in the rotorod test for neurologic deficit. The intermediate 4-nitrobenzanilides were essentially inactive in the anticonvulsant tests.

Previous studies[1] have demonstrated the high level of anticonvulsant activity associated with 4-aminobenzamides having aromatic and arylalkyl groups substituted at the amide nitrogen. Compound 1 was observed[1] to possess activity against MES- and scMet-induced convulsions in the 50 mg/kg dose range. Table II shows the anticonvulsant effects of substitution of additional alkyl groups on the aromatic ring. Compounds 1–13 all showed activity against MES-induced convulsions at 300 mg/kg 30 min after administration with most compounds, maintaining at least minimal anti-MES activity 4 h after administration. Several compounds showed some activity against scMet-induced convulsions at 30 min; however, the activity had essentially disappeared at 4 h. Each of the monomethylated anilides 2–4 exhibited anticonvulsant activity similar to 1. Only 3 showed any appreciable difference between the dosages producing toxicity and anti-MES activity.

Compounds 5–10 represent all the possible dimethylated anilides, and these compounds continue to show good anti-MES activity, with 5 and 8 being effective at 30 mg/kg. Compound 5 gave anti-MES activity in approximately half the animals tested at 30 mg/kg. Initial evaluation of compound 8 gave an indication of the high level of anticonvulsant activity associated with this compound. Thirty minutes after administration, 8 exhibited

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Table III. Quantitative Anticonvulsant Activity of Selected 4-Aminobenzanilides

compd	TD_{50}[a,b]	MES		scMET	
		ED_{50}[b]	PI[c]	ED_{50}[b]	PI[c]
1	111.30 (98.01–127.65)[d]	50.54 (40.81–59.43)[d]	2.20	59.11 (32.85–102.81)[d]	1.88
3	142.51 (130.89–161.13)	46.96 (39.77–53.41)	3.03	87.91 (62.25–111.23)	1.62
5	103.90 (88.85–119.90)	25.25 (12.50–31.75)	4.11		
8	15.01 (13.27–16.88)	2.60 (2.18–3.07)	5.77		
9	194.14 (156.61–251.07)	42.31 (38.02–50.30)	4.59	80.84 (46.85–125.93)	2.40
11	708.98 (556.77–815.69)	81.52 (56.16–105.53)	8.70		
12	>1500.0	86.13 (66.58–109.74)	>17.42		
13	49.10 (40.62–57.10)	16.67 (14.70–19.13)	2.95		
14	170.78 (153.02–189.96)	18.02 (13.41–21.43)	9.50	41.78 (38.83–46.00)	4.10
phenobarbital	69.01 (62.84–72.89)	21.78 (14.99–25.52)	3.17	13.17 (5.87–15.95)	5.24
phenytoin	65.46 (52.49–72.11)	9.50 (8.13–10.44)	6.89		
valproic acid	424.84 (368.91–450.40)	271.66 (246.97–337.89)	1.57	148.59 (122.64–177.02)	2.87

[a] Rotorod procedure. [b] Doses reported in mg/kg. [c] PI = protective index = TD_{50}/ED_{50}. [d] 95% confidence limits.

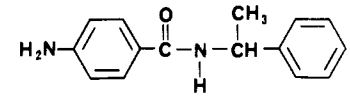
anti-MES activity and rotorod toxicity at 30 mg/kg in all animals. Four hours after administration, 8 continued to exhibit anti-MES activity at 30 mg/kg with rotorod toxicity dropping to 100 mg/kg. No anti-scMet activity was observed at either 30 min or 4 h. The testing was repeated for 8, using doses of 5, 10, 20, and 30 mg/kg, and each group of four animals subjected to the rotorod and MES tests 30 min after administration. Rotorod toxicity was observed in three of four mice given 20 mg/kg and anti-MES activity in four of four mice given 5 mg/kg of the test substance. Thus, the initial profile of anticonvulsant activity for 8 was characterized by marked ability to modify the maximal electroshock seizure pattern and inability to elevate the Metrazol seizure threshold.

The remaining three compounds 11–13 all possess an *o*-isopropyl group and present diverse activity and toxicity profiles. The compounds show excellent anti-MES activity, with 12 and 13 appearing to be more potent than 11. However, 11 and 12 show similar toxicity profiles in these preliminary studies. In contrast, compound 12 produced no rotorod toxicity in mice at a dose of 600 mg/kg while 13 showed toxicity in one out of four animals given 30 mg/kg. All animals (four of four) dosed with 13 at 300 mg/kg showed loss of righting reflex. This drastic difference in toxicity between 12 and 13 is somewhat surprising considering the structural similarity of these two compounds.

These initial screening results do not allow for any clearcut conclusions concerning structure–activity relationships. However, the anti-MES activity observed in all these compounds continues to show that these simple aromatic amides of PABA are a fruitful area for anticonvulsant research.

From the initial screening results, several compounds were selected for quantitiation of anticonvulsant and toxic effects. The results of these evaluations are given in Table III. The ED_{50} values were determined against MES- and scMet-induced convulsions, and the TD_{50} values were measured by the rotorod procedure. Quantitative data were obtained against MES-induced convulsions for all compounds; however, ED_{50}s against scMet were obtained only for compounds 1, 3, and 9. Compound 9 is the only one of the group whose anti-scMET activity produces a PI value (PI = TD_{50}/ED_{50}) greater than 2. The selectivity of effect against scMet is quite low for all three compounds as indicated by the rather low values for the slope (m) of the dose–response regression line for each compound. For example, compound 9 has m = 3.02 for anti sc-Met activity, which can be compared to m = 12.0 for anti-MES in the same compound.

A comparison of the anti-MES ED_{50} values and the TD_{50} values in Table III show the *m*-toluidine derivative, 3, to have a similar activity profile to that for the parent aniline derivative 1. Compound 8 is the most potent and most toxic of the dimethylanilines examined; however, 5, 8, and 9 all show higher PI values than the parent compound, 1. As previously discussed, the initial anticonvulsant screening studies indicated a significant degree of anti-MES activity for 8. Continued studies at lower dosing levels successfully identified the anti-MES ED_{50} for 8 at 2.6 mg/kg and the TD_{50} at 15.01 mg/kg. Compound 8 is the most potent amide of PABA observed thus far in our studies. The activity of 8 should be compared to that of compound 14 identified in a previous report[1] for its significant anti-MES activity. Compound 14, when administered ip to mice, shows a TD_{50} = 170.78 and anti-MES ED_{50} = 18.02. Thus, 8 shows an approximate 10-fold increase in toxicity and anti-MES activity in mice. However, 14 has anti-scMet activity (ED_{50} = 41.78 mg/kg) that is absent in 8.



14

The *o*-isopropyl derivatives 11 and 12 have the highest PI values of any compounds examined in this study. This is the case even with the higher anti-MES ED_{50} values. The reason for the high PI values in these two compounds appears to be the extremely high TD_{50} values, especially for 12. The toxicity evaluation of 12 places the TD_{50} value at 1500–2000 mg/kg. The drastic increase in toxicity observed between 12 and 13 as the 6-substituent of the aniline ring is altered from methyl to ethyl is a puzzling factor at this point.

The quantitiative anticonvulsant data for the 4-aminobenzanilides in Table III (especially for 8) can be compared to that for the anticonvulsant drugs phenobarbital, phenytoin, and valproic acid. The tests for these drugs were conducted in the same assay procedure. The results indicate that compound 8 possesses greater potency than any of the prototype anticonvulsants while showing a similar PI value. In most cases the slope of the regression lines for toxicity and activity are not parallel, and the PI is valid only at the dose-50 response. Thus, it is important to note the effect of slope by comparing the safety ratios (SR = TD_3/ED_{97}) for these compounds. In the MES test 8 gave an SR of 1.6, which can be compared to an SR = 2.3 for phenobarbital, SR = 3.6 for phenytoin, and SR = 0.9 for valproic acid. Compound 14 by comparison gave an SR = 3.5 in the same anti-MES test. The time of peak effect for toxicity and anti-MES activity was determined to be 30 min for 8.

The general toxicity profile for 8 was developed in mice by ip admnistration of the TD_{50}, 2 × TD_{50}, and 4 × TD_{50}

doses. The toxicity induced by the TD_{50} dose was characterized by decreased motor activity, spasticity, ataxia, rotorod toxicity, and sedation. All of these symptoms had disappeared after 2 h, and the animals appeared normal. Higher doses produced muscle relaxation, loss of righting reflex, decreased respiration with cyanosis, and ptosis in addition to the other symptoms. The animals appeared normal after 8 h. The hypnotic dose (HD_{50}) and lethal dose (LD_{50}) for **8** were determined to be 43.80 and 160.83 mg/kg, respectively. These values are significantly lower than those for phenobarbital (135.45 and 264.70 mg/kg), phenytoin (178.34 and 229.61 mg/kg), valproic acid (885.53 and 1104.62 mg/kg), and **14** (461.76 and 718.18).

The anticonvulsant activity profile for **8** was examined in a series of chemically induced seizures in mice. Amide **8** was ineffective against convulsions induced by sc metrazole, sc bicuculline, sc picrotoxin, and sc strychnine even at doses up to 30 mg/kg. Bicuculline and picrotoxin[16] induce convulsions via a GABA antagonistic effect, and strychnine blocks postsynaptic inhibition mediated by glycine.[17] Thus, **8** is ineffective by all threshold tests and exhibits an activity profile similar to that of phenytoin. In summary, **8** appears to have significant anticonvulsant activity and additional pharmacological and toxicological studies on this and related compounds are under way.

Experimental Section

Melting points were determined in open glass capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded in chloroform solutions in matched sodium chloride cells or as fluorocarbon mulls on a Beckman 4230 spectrophotometer. All ^1H NMR spectra were measured in $CDCl_3$ on a Varian T-60A spectrometer with an internal standard of tetramethylsilane. Elemental analyses (C, H, N) were performed by Atlantic Microlab Inc., Atlanta, GA.

4-Nitrobenzanilides. A solution of the appropriate alkylaniline (0.03–0.07 mol) in 35 mL of tetrahydrofuran was added to 200 mL of 20% (w/v) aqueous potassium carbonate contained in a 1-L three-necked flask equipped with a magnetic stirrer, reflux condenser, addition funnel, and a heating mantle. A solution of *p*-nitrobenzoyl chloride (2-fold molar excess) in 35 mL of tetrahydrofuran was added dropwise and the resulting mixture refluxed for 12 h and maintained at or above pH 8 during the reaction period. The solution was then cooled to room temperature and extracted with chloroform (3 × 100 mL). The extracts were combined, dried over magnesium sulfate, and evaporated. The resulting residues were purified by recrystallization from a petroleum ether (30–60 °C)–benzene mixture.

4-Aminobenzanilides. A solution of 5.0 g of the appropriate *p*-nitrobenzanilide in tetrahydrofuran or absolute ethanol was added to a Paar hydrogenation bottle along with 250 mg of 5% Palladium on carbon. The mixture was subjected to low-pressure hydrogenation (45 psi) for 3 h, and the contents of the bottle were filtered through Celite. The filtrate was evaporated and the resulting residue purified by recrystallization from benzene–petroleum ether (30–60 °C) mixtures or by column chromatography on silica gel (40 mesh) using a stepwise solvent gradient of petroleum ether (30–60 °C) and diethyl ether.

Pharmacology. Initial anticonvulsant evaluation of these compounds was conducted by using at least three dose levels (30, 100, 300 mg/kg) and in some cases a fourth dose of 600 mg/kg. All tests were performed on male Carworth Farms number-one mice. Test solutions of all compounds were prepared in 30% polyethylene glycol 400, and animals were dosed intraperitoneally 30 min prior to testing.

Maximal electroshock seizures (MES) were elicited with a 60-cycle ac of 50-mA intensity delivered for 0.2 s via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of electrodes. Abolition of the hind limb tonic extension component of the seizure was defined as protection in the MES test.

The subcutaneous pentylenetetrazole (metrazol) seizure threshold test (scMet) was conducted by administering 85 mg/kg of pentylenetetrazole as a 0.5% solution in the posterior midline. Protection in this test was defined as a failure to observe a single episode of clonic spasms of at least 5-s duration during a 30-min period following administration of the test compound.

Neurological deficit was measured in mice by the rotorod test. The dosed animal was placed on a 1-in.-diameter knurled plastic rod rotating at 6 rpm. Neurologic toxicity was defined as the failure of the animal to remain on the rod for 1 min. The median anticonvulsant potency (ED_{50}) and toxicity (TD_{50}) were determined by the graphical method.

Acknowledgment. The authors deeply appreciate the assistance of the Anticonvulsant Drug Development Program, Epilepsy Branch, NINCDS, in the pharmacological testing of these compounds. The help of Gill D. Gladding of the ADD Program is gratefully acknowledged.

Registry No. **1**, 782-45-6; **2**, 888-78-8; **3**, 63097-14-3; **4**, 955-96-4; **5**, 29027-72-3; **6**, 97042-49-4; **7**, 97042-50-7; **8**, 787-93-9; **9**, 97042-51-8; **10**, 97042-52-9; **11**, 29027-74-5; **12**, 97042-53-0; **13**, 97042-54-1; **14**, 97042-55-2; $PhNH_2$, 62-53-3; *o*-$NH_2C_6H_4Me$, 95-53-4; *m*-$NH_2C_6H_4Me$, 108-44-1; *p*-$NH_2C_6H_4Me$, 106-49-0; $NH_2C_6H_3(2,3\text{-}Me_2)$, 87-59-2; $NH_2C_6H_3(2,4\text{-}Me_2)$, 95-68-1; $NH_2C_6H_3(2,5\text{-}Me_2)$, 95-78-3; $NH_2C_6H_3(2,6\text{-}Me_2)$, 87-62-7; $NH_2C_6H_3(3,4\text{-}Me_2)$, 95-64-7; $NH_2C_6H_3(3,5\text{-}Me_2)$, 108-69-0; *o*-$NH_2C_6H_4Pr\text{-}i$, 643-28-7; $NH_2C_6H_3(2\text{-}Pr\text{-}i,6\text{-}Me)$, 5266-85-3; $NH_2C_6H_3(2\text{-}Pr\text{-}i,6\text{-}Et)$, 53443-93-9; *p*-$NO_2C_6H_4COCl$, 122-04-3.

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