Synthesis and Anticonvulsant Activity of Some *N*-Phenylphthalimides[1)]

Vincent BAILLEUX,[a,b] Louis VALLEE,[a] Jean-Pierre NUYTS,[a] and Joseph VAMECQ*,[a]

The North France Center for the Study of Childhood Epilepsy, Centre Hospitalier Universitaire et Faculté de Médecine de Lille,[a] 2, Avenue Oscar Lambret, 59037 Lille Cedex, France and School of Pharmacy, Department of Medicinal Chemistry, Université Catholique de Louvain,[b] Brussels, Belgium.

Received January 31, 1994; accepted April 14, 1994

The anticonvulsant potential of a series of *N*-phenylphthalimide derivatives has been screened in subcutaneous pentylenetetrazole seizure (scPTZ) and maximal electroshock seizure (MES) tests. Intraperitoneal 4-amino-*N*-phenylphthalimides were the most potent agents against MES in mice. Referring to the *N*-(2,6-dimethylphenyl)phthalimide structure, the order of anticonvulsant activity appears to correspond to the phthalimide ring substitution pattern of 4-amino > 4-nitro > 4-methyl; H > 3-nitro; 3-amino. The 4-amino-*N*-(2-methylphenyl)-phthalimide displays an anti-MES ED_{50} of 47.61 μmol/kg with a protective index (PI) of 4.2.

Oral administration to rats of the compounds found to be active in mice showed that the 4-amino-*N*-(2,6-dimethylphenyl)phthalimide is the most potent anti-MES agent in rats, exhibiting an ED_{50} of 25.2 μmol/kg and a PI greater than 75. Regarding the nature of the 2 and 6 substituents of the *N*-phenyl ring, the anticonvulsant efficiencies may be ordered as follows: 2,6-dimethyl > 2-methyl > 2-ethyl > 2-ethyl-6-methyl > 2,6-diethyl > unsubstituted phenyl ring.

***N*-Phenylphthalimide derivatives seem to have great potential as candidate anticonvulsant drugs.**

Keywords *N*-phenylphthalimide; electroshock; pentylenetetrazole; seizure; neurotoxicity

Epilepsy is a chronic disease characterized by epileptic seizures whose electrophysiological basis is excessive temporary neuronal discharge occurring, as a general rule, in recurrent episodes. The term is used to designate a variety of clinical epileptic disorders. For some of these disorders, gene abnormalities have been found during the course of genetic studies in families with a high incidence of epileptic patients. Recent work also indicates that increased solicitation of early protooncogene expression takes place in seizures, for instance, those induced by biccuculine.[2)] It is noteworthy that the absolute control of seizures may not be obtained with available drugs in a number of epileptic patients. The experience in our department in the last two decades has been that 5—10% of epileptic patients are refractory to all antiepileptic drugs, and a further 40%, although partially responding to therapy, are not absolutely protected by anticonvulsant treatment.

We were interested by the remarkable anticonvulsant properties of the 4-aminobenzamide series, claimed by Clark to be highly efficient anticonvulsant drugs in mice and rats.[3)] Replacing the benzamide moiety of molecules from the series of Clark with phthalimide affords *N*-phenylphthalimides. This report describes the synthesis of various *N*-phenylphthalimide derivatives and the results of an examination of their anticonvulsant activities.

Materials and Methods

Chemistry The *N*-phenylphthalimide derivatives were synthesized according to the pathways illustrated in Fig. 1. The parts A, B and C of this figure refer to the experimental procedures described in subsections A, B and C, respectively. Phthalimide, phthalic anhydride, 4-methylphthalic anhydride, 3-nitrophthalic anhydride, aniline, 2-methylaniline, 2,6-dimethylaniline, 2-ethylaniline, 2-ethyl-6-methylaniline and 2,6-diethylaniline were products of Aldrich Chemie. Melting points were determined using an electrothermal melting-point apparatus with open capillary tubes. Infrared (IR) spectra were obtained under standard operating conditions using a Beckman 4230 IR spectrophotometer. Proton NMR spectra were measured in $CDCl_3$ on a Varian T-60 A spectrometer with tetramethylsilane, as an internal standard.

A) 4-Nitrophthalic Anhydride Preparation of the 4-Nitrophthalimide: Red fuming nitric acid (90 ml) was added to 525 ml of concentrated (95—98%) sulfuric acid in a 1 l Erlenmeyer flask equipped with a

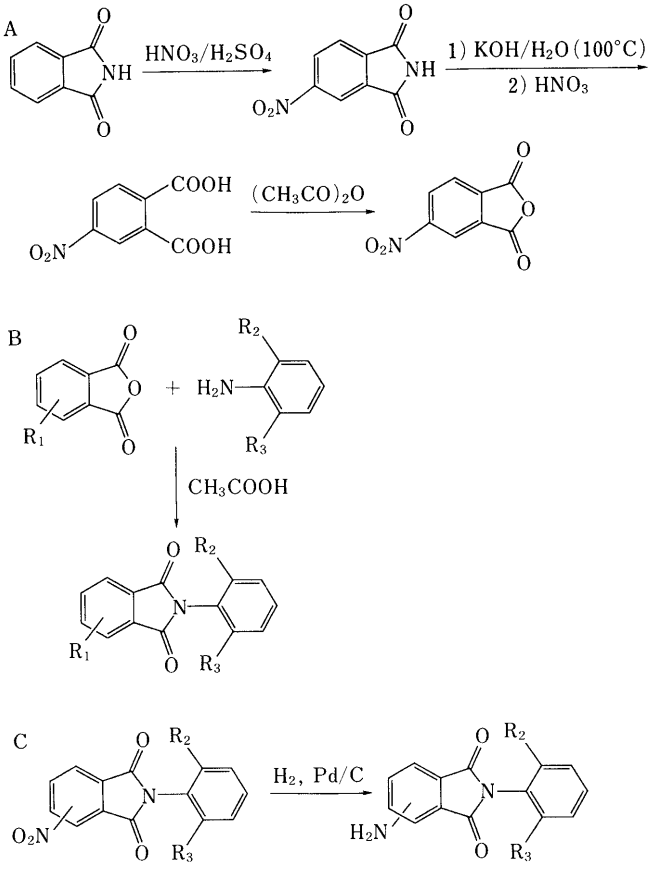


Fig. 1. Syntheses of (A) 4-Nitrophthalic Anhydride and (B, C) *N*-Phenylphthalimide Derivatives

R_1 = H, 4-CH_3, 3-NO_2, 4-NO_2; R_2, R_3 = H, CH_3 or C_2H_5.

magnetic stirrer, and the mixture was cooled in an ice bath. As soon as the temperature of the mixed acids reached 12 °C, 75 g (510 mmol) of phthalimide were stirred in as rapidly as possible while the temperature of the nitrating mixture was kept between 10 and 15 °C. The reaction mixture was allowed to warm to room temperature in the ice bath as the ice melted, and left overnight. The resulting clear, pale yellow solution was poured slowly with vigorous stirring onto 1.5 kg of ice, the temperature of this mixture never exceeding 20 °C. The crude nitration product was subsequently filtered through a Büchner funnel, and washed three times will 1 l of ice water. This material was finally purified by recrystallization from 1.5 l of 95% ethanol to afford 55 g (yield = 56%) of 4-nitrophthalimide, mp 199—201 °C.

Preparation of the 4-Nitrophthalic Acid: 4-Nitrophthalimide (80 g, 0.416 mol) was added to a solution of 37.3 g (0.66 mol) of potassium hydroxide in 240 ml of water. The mixture was heated rapidly to boiling and boiled gently for 10 min. The solution was made barely acid with 5 ml of concentrated nitric acid; after the neutral point was reached, an additional 70 ml of nitric acid was added. The solution was further boiled for 3 min, then cooled below room temperature, transferred to a 1 l separatory funnel, and extracted with two 300 ml portions of alcohol-free ether. The extract was dried over anhydrous sodium sulfate, and the ether was distilled off until a solid began to separate. The concentrated ether solution was poured into a porcelain dish and the residual solvent allowed to evaporate in a hood. The yield of 4-nitrophthalic acid which separated was 86 g (yield = 98%), mp 163—164.5 °C.

Preparation of the Anhydride: In a 250 ml round-bottomed flask equipped with a reflux condenser and a heating mantle were placed 80 g (379 mmol) of 4-nitrophthalic acid and 71.5 ml (758 mmol) of acetic anhydride. The mixture was heated to gentle boiling until 20 min after the solution became clear. After cooling, most of the solvent was removed under vacuum using a rotating evaporator. The solid was collected in a mortar and ground with 60 ml of dry, alcohol-free ether. It was filtered through a Büchner funnel, and washing was repeated twice more. The product was dried in air for a short time, and then dried to constant weight at 80 °C. The yield of 4-nitrophthalic anhydride was 64.4 g (yield = 88%), mp 118—195.5 °C.

B) *N*-(2,6-Dimethylphenyl)phthalimide, *N*-(2,6-Dimethylphenyl)-4-methylphthalimide, and 3- or 4-Nitro-*N*-phenylphthalimide Derivatives[4] An anhydride (phthalic, 4-methylphthalic, 3- or 4-nitrophthalic anhydride, 10 g), 1.5 eq of appropriate alkylaniline and 40—50 ml of acetic acid were added to a 100 ml round-bottomed flask equipped with a reflux condenser and a heating mantle. The mixture was heated to gentle boiling for 3 h. The clear solution was cooled to room temperature and diluted with 1 l of 1 N hydrochloric acid solution. A nearly white precipitate appeared which was filtered through a Büchner funnel and washed twice with 1 l of water. The crude material was recrystallized from 95% ethanol.

C) 3-Amino- and 4-Amino-*N*-phenylphthalimide Derivatives[5] In a 500 ml round-bottomed flask equipped with a reflux condenser and a heating mantle, the appropriate 3- or 4-nitro-*N*-phenylphthalimide derivative (5 g) was dissolved in isopropanol with heating. Cyclohexene (50 ml) and 1 g of 10% Pd/C were added to the solution and the mixture was heated to boiling for 5 h. Then the mixture was cooled to room temperature and the catalyst removed by filtration. The filtrate was evaporated under vacuum using a rotating evaporator, and the crude material was recovered. The 3-amino-*N*-phenylphthalimide derivatives were recrystallized from 95% ethanol and the 4-amino-*N*-phenylphthalimide derivatives were recrystallized from ethanol/water.

Anticonvulsant Tests Initial anticonvulsant evaluation of the *N*-phenylphthalimide derivatives was conducted by following the Anticonvulsant Drug Development (ADD) Program protocol.[6] Male albino mice (CF-1 strain, 18—25 g; Charles River, Wilmington, MA, U.S.A.) and male albino rats (Sprague-Dawley, 100—150 g; Simonsen, Gilroy, CA, U.S.A.) were used as experimental animals. The animals were allowed free access to food (S/L Custom Lab Diet-7) and water, except when removed from their cages for the experimental procedures.

All compounds were suspended in 0.5% methylcellulose/water mixture. They were administered either orally (0.04 ml/10 g to rats) or intraperitoneally (0.01 ml/g body weight to mice). All tests were conducted at the previously determined time of peak drug effect (TPE). To determine anticonvulsant potency and toxicity, groups of at least eight mice or rats were tested with various doses of the compound until at least four doses were established between the limits of 100% and 0% protection or toxicity. The doses of drug required to produce the desired endpoint in 50% of animals (ED_{50}) or minimal neurological toxicity in 50% of animals (TD_{50}), and the respective 95% confidence intervals, were calculated by means of a computer program using probit analysis.

The profile of anticonvulsant activity for each substance was established by one electrical and one chemical test.

The electrical test employed was the maximal electroshock seizure (MES) pattern test. In this test, maximal seizures are elicited by a 60 Hz alternating current in 50 mA (mice) or 150 mA (rats) delivered for 0.2 s *via* corneal electrodes. This amount of current is approximately six times the threshold and reveals the ability of the compound to prevent seizure spread. A drop of 0.9% sodium chloride solution instilled in each eye prior to application of the electrodes ensures adequate electrical contact; it also reduces the incidence of fatalities to near zero. Maximal seizures are produced in all normal mice. The maximal seizure typically consists of a short period of initial tonic flexion and a prolonged period of tonic extension (especially of the hind limbs) followed by terminal clonus. The typical seizure lasts approximately 22 s. Failure to extend the hind limbs to an angle with the trunk greater than 90° is defined as protection.

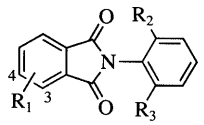
The chemical test employed is the subcutaneous pentylenetetrazole (scPTZ) seizure threshold test. This test actually measures the ability of anticonvulsants to afford complete protection against threshold seizures induced by subcutaneous injection of pentylenetetrazole at the CD_{97} values (85 and 70 mg/kg in mice and rats, respectively). In practice, pentylenetetrazole was dissolved in sufficient 0.9% sodium chloride solution to allow subcutaneous injections to mice and rats of volumes of 0.01 and 0.02 ml/g body weight, respectively. A minimal time period of 30 min subsequent to subcutaneous administration of pentylenetetrazole was used for seizure detection, protection being defined as failure to observe an episode of clonic spasm of at least 5 s duration during this time period.

Neurotoxicity Tests The median minimal neurotoxic dose (TD_{50}) in mice was determined by the rotorod procedure. The mouse is placed on a 1 inch diameter knurled plastic rod rotating at 6 rpm. Normal mice can remain indefinitely on a rod rotating at this speed. Neurological deficit (*e.g.*, ataxia, sedation, hyperexcitability) is indicated by the inability of the animal to maintain equilibrium on the rod for at least 1 min in each of three trials. Neurological deficit in rats was indicated by ataxia, loss of placing response, and muscle tone.

Results

Table I lists the structure, melting point, percentage

TABLE I. Physical Properties of *N*-Phenylphthalimides[a]



Compd.	R_1	R_2	R_3	mp (°C)	Yield (%)	Formula
1	H	CH_3	CH_3	206—207	66	$C_{16}H_{13}NO_2$
2	4-CH_3	CH_3	CH_3	143—145	56	$C_{17}H_{15}NO_2$
3	3-NO_2	CH_3	H	152—153	77	$C_{15}H_{10}N_2O_4$
4	3-NO_2	CH_3	CH_3	172—174	76	$C_{16}H_{12}N_2O_4$
5	3-NH_2	CH_3	H	197—199	51	$C_{15}H_{12}N_2O_2$
6	3-NH_2	CH_3	CH_3	225—228	51	$C_{16}H_{14}N_2O_2$
7	4-NO_2	H	H	191—193	95	$C_{14}H_8N_2O_4$
8	4-NO_2	CH_3	H	166—168	80	$C_{15}H_{10}N_2O_4$
9	4-NO_2	CH_3	CH_3	176—179	75	$C_{16}H_{12}N_2O_4$
10	4-NO_2	C_2H_5	H	137—138	74	$C_{16}H_{12}N_2O_4$
11	4-NO_2	C_2H_5	CH_3	163—165	78	$C_{17}H_{14}N_2O_4$
12	4-NO_2	C_2H_5	C_2H_5	141—143	85	$C_{18}H_{16}N_2O_4$
13	4-NH_2	H	H	209—210	57	$C_{14}H_{10}N_2O_2$
14	4-NH_2	CH_3	H	189—190	52	$C_{15}H_{12}N_2O_2$
15	4-NH_2	CH_3	CH_3	195—198	51	$C_{16}H_{14}N_2O_2$
16	4-NH_2	C_2H_5	H	152—154	40	$C_{16}H_{14}N_2O_2$
17	4-NH_2	C_2H_5	CH_3	177—180	45	$C_{17}H_{16}N_2O_2$
18	4-NH_2	C_2H_5	C_2H_5	173—175	58	$C_{18}H_{18}N_2O_2$

a) The IR and NMR (^1H) spectra were consistent with structural assignments.

TABLE II. Anticonvulsant and Toxicity Screening Data in Mice Dosed Intraperitoneally

Compound	MES		scPTZ		Toxicity	
	30 min	4 h	30 min	4 h	30 min	4 h
1	++	−	−	−	−	−
2	++	+	+	+	+	+
3	−	−	−	−	−	−
4	−	+	−	−	−	−
5	−	−	−	−	−	−
6	−	−	−	−	−	−
7	−	−	−	−	−	−
8	++	−	−	−	−	−
9	++	++	−	+	−	+
10	++	−	−	−	−	−
11	−	+	−	−	−	−
12	−	++	−	−	−	−
13	++	++	−	+	−	+
14	+++	++	++	−	++	+
15	+++	++	+++	−	++	+
16	++	++	++	+	++	+
17	++	++	−	+	+	+
18	++	+	−	−	−	−

+++, ++ and + signify activity at 30, 100 and 300 mg/kg, respectively; − denotes no activity observed at 300 mg/kg. Toxicity was determined by the rotorod test. The anticonvulsant and neurotoxicity tests were performed after 30 min and 4 h.

yield and formula of each of the 18 *N*-phenylphthalimides as well as the numbers assigned to them in the text. These compounds were evaluated for anticonvulsant activity in mice, and the active compounds in mice were further evaluated in rats.

Studies on Mice Initial Screening: Initial screening for anticonvulsant activity and toxicity in mice dosed intraperitoneally is documented in Table II. Compound **1** showed some activity against MES seizures at 100 mg/kg. The 4-methyl derivative (**2**) exhibited anti-MES activity at 100 mg/kg and activity against scPTZ seizures at 300 mg/kg. The 3-nitro- or 3-amino-*N*-phenylphthalimide derivatives (**3**—**6**) were essentially inactive except for compound **4**, which exhibited slight anti-MES properties at 300 mg/kg after 4 h. The 4-nitro-*N*-phenylphthalimide derivatives displayed anti-MES activity at 100 mg/kg (**8**—**10**, **12**) except for **7**, which, under our experimental conditions, was inactive and **11**, whose anti-MES activity required a 300 mg/kg dose. The 4-amino-*N*-phenylphthalimide derivatives (**13**—**18**) were the most active but also toxic in this initial screening. Compounds **14** and **15** showed anti-MES activity at 30 mg/kg and rotorod toxicity at 100 mg/kg with loss of righting reflex at 300 mg/kg. For compound **15**, activity against scPTZ seizures was recorded at 30 mg/kg after 30 min while a continuous seizure activity was observed at 100 and 300 mg/kg. No rotorod toxicity was observed in any of the animals dosed with compound **18** at either level.

Quantitative Evaluation: From the anti-MES screening results, compounds **14**, **15** and **18** were chosen for quantitative evaluation against MES-induced convulsions in mice; Table III shows the results of this study. Compound **15** gave an anti-MES ED_{50} of 49.5 μmol/kg and a TD_{50} of 130.61 μmol/kg, yielding a PI of 2.6. This compound was ineffective against scPTZ at less than toxic doses; among eight mice dosed with 50 mg/kg (188 μmol/kg) of **15**, three exhibited continuous seizure activity in the scPTZ test after 30 min. Compounds **14** and **18** were found to be as active and less toxic than **15**. The anti-MES ED_{50} of 51.41 μmol/kg for **18** with a TD_{50} of 206.26 μmol/kg resulted in a PI of 4. Compound **14** gave an anti-MES ED_{50} of 47.61 μmol/kg and a TD_{50} of 200.56 μmol/kg, yielding a PI of 4.2.

TABLE III. Quantitative Anticonvulsant Data in Mice Dosed Intraperitoneally

Compound	TPE (MES) (min)	ED_{50} (MES)	TPE (Tox) (min)	TD_{50}	PI
14	15	47.61 (36.5—61.7)	15	200.56 (121.8—331.7)	4.2
15	30	49.5 (42.3—59.1)	15	130.61 (112.3—152.7)	2.6
18	15	51.41 (42.7—62.6)	15	206.26 (161.9—254.5)	4

Values reported are in μmol/kg of body weight; 95% confidence intervals in parentheses. TD_{50} was determined by the rotorod procedure. Anticonvulsant and neurotoxicity tests were performed at the TPE.

TABLE IV. Anticonvulsant [Anti-MES] and Toxicity Screening Data in Rats Dosed Orally

Compound	15 min	30 min	1 h	2 h	4 h
1	2/4	2/4	0/4	1/4	2/4
2	1/4	1/4	1/4	0/4	0/4
8	1/4	1/4	1/4	1/2	—
9	3/4	3/4	3/4	0/4	4/4
10	0/4	1/4	1/4	1/4	3/4
11	1/4	2/4	3/4	2/4	2/4
12	1/4	1/4	2/4	1/4	3/4
13	2/4	2/4	0/4	2/4	1/4
14	4/4	4/4	4/4	4/4	3/4
15	4/4	4/4	4/4	3/4	2/4
16	4/4	4/4	4/4	4/4	2/4
17	2/4	3/4	4/4	3/4	0/2
18	3/4	3/4	4/4	4/4	3/4

Rats were given a single dose of 50 mg/kg. Ratios of protected animals to tested animals (routinely four animals were tested for one compound at one time point) in the MES test after 15, 30 min, 1, 2 and 4 h are indicated. No toxicity was observed at this dose.

Studies on Rats Initial Screening: Initial anti-MES activity data in rats dosed *p.o.* with 50 mg/kg of several *N*-phenylphthalimides are summarized in Table IV. No toxicity was observed at this dose for any compound. The 4-amino-*N*-phenylphthalimides (**14**—**18**) showed the most potent anticonvulsant activity; all the animals dosed with **14**, **15** or **16** were protected against MES from 15 min to 1 h. Compound **13** which has an unsubstituted *N*-phenyl ring, was found to be much less active than the other 4-amino derivatives. From the 4-nitro-*N*-phenylphthalimides (**8**—**12**), compound **9** was then more effective against MES.

Quantitative Evaluation: From the initial screening results, compounds **9**, **14**, **15**, **16**, **17** and **18** were chosen for quantitative evaluation of anticonvulsant activities and toxic effects in rats dosed *p.o.* The results of these evaluations are given in Table V. In the neurotoxicity test, all doses were tested at 15 min through 24 h, except for

TABLE V. Quantitative Anticonvulsant Data in Rats Dosed Orally

Compound	TPE (MES)	ED_{50} (MES)	Time (Tox)	TD_{50}	PI
9	1 h	87.92 (55—121.9)	15 min→ 24 h	>1688	>19.2
14	30 min	35.44 (22.2—52.5)	15 min→ 24 h	>350	>10
15	15 min	25.2 (17.2—38)	15 min→ 24 h	>1900	>75
16	15 min	72.81 (40.5—109.1)	2 h	>1390	>19
17	30 min	85.2 (61.3—104.5)	15 min→ 24 h	>1800	>21
18	2 h	132.67 (68.1—246.1)	15 min→ 24 h	>1000	>7.6

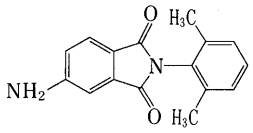
Values reported are in μmol/kg of body weight; 95% confidence intervals in parentheses. Neurotoxicity was indicated by ataxia and loss of placing response and muscle tone. The MES test was performed at the TPE, neurotoxicity was observed from 15 min to 24 h, except for compound **16**.

compound **16**. Compound **15** was found to be the most active; it gave an anti-MES ED_{50} of 25.2 μmol/kg and a TD_{50} > 1900 μmol/kg, yielding a PI > 75. Thus, **15** shows a high level of anticonvulsant activity and a wide therapeutic window as indicated by the very high PI. The 4-nitro compound **9** was less active than **15** and gave an anti-MES ED_{50} of 87.92 μmol/kg and a TD_{50} > 1688 μmol/kg, yielding a PI > 19.2. The other 4-amino compounds tested also gave high TD_{50} and PI. No anti-scPTZ activity was apparent at the doses used; for example, rats dosed orally with 940 μmol/kg of **15** were not protected against scPTZ-induced convulsions.

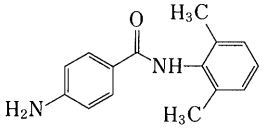
Discussion

Most of the *N*-phenylphthalimides tested displayed anticonvulsant (anti-MES, mainly) properties with the exception of 3-nitrophthalimide (compounds **3**, **4**) and 3-aminophthalimide (compounds **5**, **6**) derivatives, suggesting that substitution of the phthalimide moiety in position 3 (*versus* the absence of substitution, *cf.* compound **1**) leads to the loss of anticonvulsant properties. Substituting the phthalimide moiety in position 4 has an opposite effect and affords highly potent anticonvulsant compounds in the case of a primary amine as the substituted group. Although less active than the 4-amino derivatives, the 4-methyl- and 4-nitrophthalimides also display anticonvulsant properties. Regarding the *N*-(2,6-dimethylphenyl)phthalimide derivatives (**1**, **2**, **4**, **6**, **9**, **15**) tested in mice, the order of decreasing anticonvulsant activity in relation to the phthalimide ring substitution pattern was: 4-amino > 4-nitro > 4-methyl; H > 3-nitro; 3-amino. On the other hand, in rats, the relationship between anti-MES activity of the 4-amino-*N*-phenylphthalimides and the groups at positions 2 and 6 of the *N*-phenyl ring was: 2,6-dimethyl > 2-methyl > 2-ethyl > 2-ethyl-6-methyl > 2,6-diethyl > unsubstituted phenyl ring. In addition to the hydrophobicity they are expected to confer on the parent compounds, it would not be surprising if these alkyl groups play a role in modifying the relative orientation of the phthalimide and the *N*-phenyl rings.

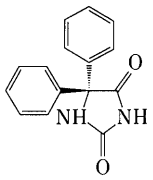
Compound **15** appears to possess the greatest anti-



4-ADMPP (ADD213063)



4-ADMPB (LY201116)



phenytoin

Fig. 2. Chemical Structure of 4-ADMPP, 4-ADMPB and Phenytoin

convulsant potential of the present *N*-phenylphthalimide series. In mice dosed intraperitoneally, compounds **14** and **18** appear to exhibit a comparable potential but with a better PI than **15**. Nevertheless, in rats, **15** appears to be the most interesting anti-MES agent in terms of not only the ED_{50}, but also TPE, TD_{50} and PI. Fig. 2 compares the formulae of compound **15**,[7] 4-ADMPB (the most potent anticonvulsant member of the 4-aminobenzamide series developed by Clark and colleagues), and phenytoin, a drug of choice for most types of epileptic disorders. As is clear, compound **15** and 4-ADMPB, which are the most potent anticonvulsant members of their series (*i.e.* *N*-phenylphthalimide and *N*-phenylbenzamide series, respectively) both have two phenyl rings, the amino function in position 4 of one of the two phenyl rings and substitution of the other phenyl ring, in positions 2 and 6, by two methyl groups. The relation of phenytoin to the two above-mentioned structures might appear less obvious, but it is noteworthy that compound **14**, whose anticonvulsant properties are similar to those of compound **15** (see Tables III, V), and phenytoin are isomers, having the same molecular formula, namely $C_{15}H_{12}N_2O_2$. The assay of phenytoin using the same procedure as that utilized in the present work gave an anti-MES ED_{50} of 118.1 μmol/kg and a TD_{50} > 12000 μmol/kg in rats dosed orally, yielding a PI > 100.[8] The corresponding values for 4-ADMPB amount to 135.2 and 1909.7 μmol/kg, respectively, with PI = 14.1.[8] Thus, compound **15** appears to be more active than phenytoin and 4-ADMPB in the anti-MES test in rats dosed orally. It represents a valuable lead compound for the design of anticonvulsant drugs.

Compound **15** has also been tested in four chemically induced seizure models, in mice dosed intraperitoneally,[9] *i.e.*, the subcutaneous bicuculline seizure threshold test, the subcutaneous picrotoxin seizure threshold test, the subcutaneous strychnine seizure pattern test, and the intravenous pentylenetetrazole seizure threshold test (the authors, unpublished work). Further comparison of the

anticonvulsant activity profiles of **15** and antiepileptic drug prototypes (*i.e.*, phenytoin, carbamazepine, phenobarbital, ethosuximide, felbamate, and sodium valproate) in mice and rats, following the ADD program, has confirmed that compound **15**, like phenytoin and carbamazepine, is mainly active, at non toxic doses, against MES-induced seizures. Phenytoin and carbamazepine are thought to exert their anticonvulsant effects mainly by blocking brain sodium channels.[10] Several drug-binding, ion-flux, and electrophysiological studies have demonstrated that these two antiepileptic drugs produce a voltage-dependent block of sodium channels in mammalian neurons at therapeutically relevant concentrations.[11-15]

In conclusion, 4-ADMPP (compound **15**) is a potent and selective anti-MES agent and thus prevents seizure spread. Interaction of this compound with neuronal sodium channels will be the subject of appropriate studies in the near future.

Acknowledgments The authors deeply appreciate the assistance of the ADD Program, Epilepsy Branch, Division of Convulsive, Developmental and Neuromuscular Disorders (National Institutes of Health, Bethesda, MD, U.S.A.), in the testing of these compounds. The help of James P. Stables of the ADD Program is gratefully acknowledged. V.B. is sponsored by the Conseil Régional du Nord-Pas de Calais and the Centre Hospitalier Universitaire de Lille (France). J.V. is Chargé de Recherches Première Classe from the French INSERM. The present work was supported by grants from the Comité Directeur de la Recherche (Faculty of Medicine and University Hospital of Lille, France).

References and Notes

1) Abbreviations: MES, maximal electroshock seizure; scPTZ, subcutaneous pentylenetetrazole seizure threshold test; ED_{50}, dose providing anticonvulsant protection in 50% of the animals tested; TD_{50}, dose inducing neurotoxicity in 50% of the animals tested; PI, protective index (equal to the TD_{50} to ED_{50} ratio); TPE, time of peak drug effect; CD_{97}, dose calculated to produce convulsions in 97% of the animals tested; 4-ADMPB, 4-amino-*N*-(2,6-dimethylphenyl)benzamide.
2) P. Gass, T. Herdegen, R. Bravo, M. Kiessling, *Neuroscience*, **48**, 315 (1992).
3) C. R. Clark, M. J. M. Wells, R. T. Sansom, G. N. Norris, R. C. Dockens, W. R. Ravis, *J. Med. Chem.*, **27**, 779 (1984); C. R. Clark, R. T. Sansom, C. M. Lin, G. N. Norris, *ibid.*, **28**, 1259 (1985); C. R. Clark, C. M. Lin, R. T. Sansom, *ibid.*, **29**, 1534 (1986); C. R. Clark, T. W. Davenport, *J. Pharm. Sci.*, **76**, 18 (1987); *idem*, *J. Med. Chem.*, **30**, 1214 (1987).
4) Compounds enumerated **1** to **4** and **7** to **12** in Table I, Results section.
5) Compounds enumerated **5**, **6** and **13** to **18** in Table I, Results section.
6) R. L. Krall, J. K. Penry, B. G. White, H. J. Kupferberg, E. A. Swinyard, *Epilepsia*, **19**, 409 (1978).
7) This compound could be termed 4-ADMPP [4-amino-*N*-(2,6-dimethylphenyl)phthalimide].
8) C. R. Clark, *Epilepsia*, **29**, 198 (1988).
9) P. P. De Deyn, R. D'Hooge, B. Marescau, Y. Pei, *Epilepsy Res.*, **12**, 87 (1992).
10) R. L. Macdonald, K. M. Kelly, *Epilepsia*, **34** (Suppl. 5), S1 (1993).
11) J. Francis, W. McIntyre Burnham, *Mol. Pharmacol.*, **42**, 1097 (1992).
12) D. S. Ragsdale, T. Scheuer, W. A. Catterall, *Mol. Pharmacol.*, **40**, 756 (1991).
13) D. J. Schwarz, G. Grigat, *Epilepsia*, **30**, 286 (1989).
14) M. Willow, T. Gonoi, W. A. Catterall, *Mol. Pharmacol.*, **27**, 549 (1985).
15) M. Willow, W. A. Catterall, *Mol. Pharmacol.*, **22**, 627 (1982).