Molecular Representation. Figures 2, 3, and 5 were generated on the Abbott CAMD computer graphics system[24] using the Cartesian coordinates of Fesik et al.[15a] The molecular surface was calculated by using Connolly's MS surface program.[25] The pictures were taken directly from the Evans & Sutherland MPS terminal screen connected to a VAX 11/785 computer.

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Synthesis and Anticonvulsant Properties of 2,3,3a,4-Tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones

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A series of 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones were synthesized and evaluated for anticonvulsant activity in DBA/2 mice against sound-induced seizures and in rats against maximal electroshock-induced seizures. Most of the derivatives showed an anticonvulsant effect better than that of valproate, a commonly used anticonvulsant drug. Compound **3** possessed an anticonvulsant activity comparable to that of diphenylhydantoin in both tests and was selected for further studies. Structure–activity relationships are discussed.

The need for improved agents for the treatment of seizure disorders is widely recognized. The therapeutic efficacy of available antiepileptic drugs cannot be defined as totally satisfactory, and moreover the most marketed anticonvulsants possess a broad range of undesiderable side effects. This warrants the continuing research for antiepileptic drugs with more selective anticonvulsant activity and lower toxicity.

Drugs clinically active against epilepsy include derivatives with structural similarities. The most common structural elements appear to be a nitrogen heteroatomic system and at least one carbonyl group. Most of them also have at last one phenyl group and either another phenyl ring or an alkyl substituent attached to the heteroatomic system.

As part of our program on the chemistry of heteropolycyclic systems[1-4] as potential pharmacological agents, we reported[2,3] the synthesis and identification of a series of 2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones in which all of the above-mentioned structural characteristics were present.

We now report here the synthesis of new derivatives and the evaluation of anticonvulsant activity of all hitherto synthesized pyrrolo[1,2-*a*]benzimidazolones. This study was performed in an effort to elucidate the relationship between the pyrrolobenzimidazolone structure and the anticonvulsant activity and to determine the optimal substitution pattern in the tricyclic system. To our knowledge no member of this chemical class has been tested as an anticonvulsant agent.

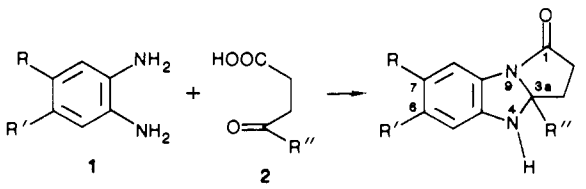
The title compounds were evaluated for anticonvulsant activity in DBA/2 mice against sound-induced seizures and in rats against maximal electroshock-induced seizures (MES).

Results and Discussion

The compounds employed in this study were prepared according to reported procedures[2,3] (Scheme I).

Synthesis of the new compounds **5** and **6** was carried out by reacting 1,2-phenylenediamine **1** with 3-acylpropionic acids **2** in boiling toluene with azeotropic removal of water. The obtained products were isolated by flash chromatography and characterized by spectroscopic methods.

Scheme I



1 2 3-18

	R	R′	R″
3	H	H	CH_3
4	H	H	C_6H_5
5	H	H	4-Cl-C_6H_4
6	H	H	4-F-C_6H_4
7	H	Cl	CH_3
8	Cl	H	CH_3
9	H	Cl	C_6H_5
10	Cl	H	C_6H_5
11	H	Cl	4-Cl-C_6H_4
12	Cl	H	4-Cl-C_6H_4
13	H	Cl	4-F-C_6H_4
14	Cl	H	4-F-C_6H_4
15	H	CH_3	CH_3
16	CH_3	H	CH_3
17	H	NO_2	CH_3
18	NO_2	H	CH_3

In the ^1H NMR spectra of the synthesized compounds (Table I), the alicyclic region was characterized by an ABCD-like system analyzed by means of the LAOCN3 program.[5] Protons at the C-2 atom were assigned as the nearest to the carbonyl group on the basis of their smaller

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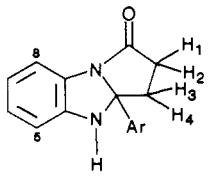
Table I. Physical Properties and ^1H NMR Data for New 2,3,3a,4-Tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-ones **5** and **6**



compd	mp, °C	yield,[a] %	formula[b]	ν_1	ν_2	ν_3	ν_4	ν_5	ν_8	NH	Ar
5	147–149	52	$C_{16}H_{13}ClN_2O$	2.52 ($J_{1,2}$ = 17.0, $J_{1,3}$ = 11.8, $J_{1,4}$ = 8.0)	2.45 ($J_{2,3}$ = 8.2, $J_{2,4}$ = 1.3)	2.68 ($J_{3,4}$ = 13.1)	2.73	6.63	7.32	4.28	6.50–7.28
6	128–130	48	$C_{16}H_{13}FN_2O$	2.51 ($J_{1,2}$ = 17.1, $J_{1,3}$ = 12.3, $J_{1,4}$ = 8.1)	2.43 ($J_{2,3}$ = 8.2, $J_{2,4}$ = 1.2)	2.65 ($J_{3,4}$ = 13.2)	2.70	6.44	7.50	4.55	6.51–7.46

[a] Based upon recrystallized yields. [b] All compounds gave satisfactory analyses for C, H, N (±0.4%).

geminal coupling and because the addition of lanthanide complex Eu(fod)$_3$ induced a considerable downfield shift on their signals as a consequence of the complexation at the carbonyl group.

The resonance pattern of the aromatic moiety were unambiguously assigned by NOE measurements.[6] The signals of the hydrogen atoms in ortho position to the NH appeared upfield as a consequence of the mesomeric effect of the amino group while the 8-H resonated at lower fields due to the deshielding effects of the amidic nitrogen at position 9 of the system. The application of nuclear Overhauser effect difference spectroscopy confirmed the assignment: the irradiation to the NH proton resulted in an enhancement of the signals for 5-H.

Table II summarizes the data of anticonvulsant activity observed after intraperitoneal administration of the title compounds. In order to better characterize the possible anticonvulsant activity of our compounds, we used two different tests (i.e. maximal electroshock-induced and sound-induced seizures). The first test has been largely used for screening of compounds that showed specific activity in grand mal and partial seizures,[7] whereas the second test was very sensitive for compounds acting also on the primary absence.[8]

To explore whether the substitution at the 6- or 7- and 3a-positions was responsible for the observed activity, we employed compounds with different substituents. Compounds **6**, **17**, and **18** showed no anticonvulsant properties against maximal electroshock-induced and sound-induced seizures at varying dose levels up to 600 μmol/kg. A moderate antiseizure activity after ip administration of **4**, **11**, **12**, and **16** was observed while a significant anticonvulsant activity was seen after ip injection of **5**, **8**, **10**, **14**, and **15**. More active were the compounds **7**, **9**, and **13** in which a chlorine atom is present at position 6. Derivative **3** was the most active compound of this series of pyrrolobenzimidazolones. It completely protected against the clonic seizure phase at doses as low as 100 μmol/kg in DBA/2 mice and completely antagonized the tonic hind limb extension in the MES test at a 200 μmol/kg dose in rats. It is remarkable to note that our compounds showed a better anticonvulsant activity than the clinically useful anticonvulsant sodium valproate.[7] Furthermore, compound **3** possessed an anticonvulsant effect comparable to that of diphenylhydantoin[7] (Table II).

Table II. Anticonvulsant Activity against Maximal Electroshock Seizures (MES) in Rats and against Audiogenic Seizures in DBA/2 Mice of Compounds **3**–**18** and Their Relative Lipophilicity (R_M)[a]

compd	electroshock: ED_{50}, μmol/kg	audiogenic seizures, clonic phase: ED_{50}, μmol/kg	R_M
3	35.5 (25.2–50)	26.3 (15.8–43.6)	−0.341
4	199.5 (164.2–241.4)	161.4 (130.5–196)	−0.131
5	234.4 (180.3–303.7)	166.0 (144.3–191)	−0.033
6	575.4 (491.8–674)	356.3 (307.1–421.8)	−0.084
7	88.2 (68.4–113.7)	79.4 (60.2–104.6)	−0.167
8	233.9 (193.3–282.8)	147.9 (131.5–166.4)	−0.162
9	125.9 (111.4–142.8)	95.9 (85.2–107.9)	−0.007
10	271.2 (235.7–308.3)	179.1 (154.4–207.4)	−0.005
11	281.1 (223.2–353.4)	143.3 (134.0–154.0)	0.068
12	501.2 (424.7–589.3)	346.7 (301.5–398.8)	0.073
13	105.1 (81.8–135.3)	87.3 (76.5–99.3)	0.019
14	198.5 (171.1–230.5)	177.8 (145.8–216.3)	0.028
15	141.3 (117.1–171.5)	97.7 (90.5–105.3)	−0.284
16	197.4 (167.6–232.5)	121.7 (98.2–150.9)	−0.279
17	>600	>600	−0.187
18	>600	>600	−0.237
valproate	1886 (1456–2301)[b]	1234.0 (987.1–1543)	
diphenyl-hydantoin	55.5 (39.7–75.4)[b]	19.8 (17.7–22.3)	

[a] All compounds were administered ip as a water solution of dimethyl sulfoxide (80% DMSO and 20% distilled water). ED_{50} values (±95% confidence limits) were calculated according to the method of ref 15. [b] Data from ref 7.

The results we have obtained suggest that derivative **3**, the most active compound of our series, has no substituent on the aryl moiety. Among the 6- and 7-substituted derivatives, the maximal activity is obtained when in the pyrrolobenzimidazolone system is present a chlorine atom at position 6 while substitution at C-7 by the same substituent decreases potency, which is also reduced by a methyl group at the 6- or 7-position. The presence of a nitro group at the same positions destroys activity in both tests used. No correlation was observed between the activity and the nature of the substituent at the 3a-position.

The variant degree of anticonvulsant activity exhibited by these compounds cannot be directly related to their lipophilicity (Table II). In fact, derivatives bearing a nitro group at the 6- or 7-position, which possess a relative lipophilicity (R_M) comparable to that of the more active compounds of our series, showed no anticonvulsant activity, suggesting the importance of other parameters. Moreover, 6-substituted derivatives are generally more active than 7-substituted isomers with similar lipophilic characteristics. It is possible that their different anticonvulsant potency is due to a different affinity for the carrier system that transfers these compounds through to the blood–brain barrier and provides an easier access to

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the central nervous system for the 6-chloro-substituted derivatives and compound 3.

Like other anticonvulsant drug (i.e. diphenylhydantoin and valproate) our compounds affected motor movements. In particular, at the high dose levels used, they produced a reduction of locomotor activity and sedation both in mice and rats. Ataxia, fall in rectal temperature, and splayed hind limbs were observed only in DBA/2 mice. In both mice and rats the title compounds appeared less toxic than diphenylhydantoin but similar in toxicity to or more toxic than valproate.

Experimental Section

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The structures of new adducts were deduced from spectroscopic data (IR, ^{1}H NMR, and MS) and supported by satisfactory elemental analysis. Elemental analysis indicated by symbols of the elements refer to data within ±0.4% of the theoretical values. Precoated Merck silica gel 60 F_{254} plates were used for TLC. Flash chromatography was performed with thick-walled glass column on silica gel (Merck, 32–63 μm) according to the method reported by Still et al.[9] Infrared spectra were recorded in hexachlorobutadiene on a Perkin-Elmer Model 257 spectrophotometer and exhibited a characteristic absorption maximum for the carbonyl stretching and the band related to the NH group. ^{1}H NMR spectra were obtained with a Bruker WP 200 spectrometer in $CDCl_3$ (internal lock) with TMS as the internal standard: chemical shifts are in δ (ppm) and coupling constants (J) in hertz. NH was identified by deuteriation. Eu(fod)$_3$ was used as a lanthanide shift reagent (LSR) and was added stepwise; each signal was followed in the spectra. The ABCD pattern was analyzed with the aid of a version of the LAOCN3 program modified by us to run on an IBM computer and to include a subroutine for plotting calculated spectra on a line printer (the rms error was 0.025). NOE measurements were performed by the FT difference method on carefully degassed $CDCl_3$ solutions of the synthesized compounds. Mass spectra were recorded on a Hewlett-Packard Model 5995 A GC/MS: the molecular ions were present and the fragmentation were consistent with the assigned structure.

3a-(4-Chlorophenyl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one (5). To a solution of 1,2-phenylenediamine (2.7 g, 0.025 mol) in anhydrous toluene (40 mL) was added, with stirring at room temperature, a solution of 3-(4-chlorobenzoyl)propionic acid (5.3 g, 0.025 mol) in 20 mL of the same solvent. The reaction mixture was refluxed for 6 h with a Dean–Stark apparatus. After removal of the solvent in vacuo, the residue was subjected to flash chromatography on a silica gel column using CCl_4 as eluant with an increasing amount of ethyl acetate up to a ratio of 8:2 v/v. Recrystallization from ethyl acetate gave a compound melting at 147–149 °C (yield 52%). IR: 3240 and 1690 cm^{-1}. MS, m/z: 284 (M$^+$, 32), 283 (15), 229 (100), 228 (42), 173 (76), 131 (30), 92 (22), 76 (14), 64 (16).

3a-(4-Fluorophenyl)-2,3,3a,4-tetrahydro-1*H*-pyrrolo[1,2-*a*]benzimidazol-1-one (6). Compound **6** was obtained according to the same procedure employed for compound **5** with 3-(4-fluorobenzoyl)propionic acid (4.9 g, 0.025 mol) and 1,2-phenylenediamine (2.7 g, 0.025 mol) as starting materials. The obtained compound, after recrystallization with ethyl acetate, melted at 128–130 °C (yield 48%). IR: 3295 and 1705 cm^{-1}. MS, m/z: 268 (M$^+$, 35), 267 (18), 213 (100), 212 (87), 173 (78), 131 (35), 122 (11), 95 (12), 92 (23), 76 (11), 64 (19).

Lipophilicity Measurements. The relative lipophilicity of the compounds was measured by reversed-phase thin-layer chromatography according to the method described in literature.[10,11]

Silanized silica gel plates Merck 60 F_{254} were used as nonpolar stationary phase. The plates were dried at 105 °C for 1 h before use. The polar mobile phase was a 2:1 v/v mixture of acetone and water. Each compound was dissolved in chloroform (3 mg/mL), and 5 μL of the solution was applied onto the plate. The experiments were repeated five times with different disposition of the compounds on the plate. The R_f values were expressed as the mean values of the five determinations. The R_M values were calculated from the experimental R_f values according to the formula $R_M = \log [(1/R_f) - 1]$. Higher R_M values indicate higher lipophilicity (Table II).

Pharmacological Methods. Adult male Wistar rats (200–250 g; Charles River, Calco, Como) and DBA/2 mice of either sex (6–12 g; 21–25 days old; Charles River, Calco, Como) were used for pharmacological studies. The compounds were administered ip as a water solution of dimethyl sulfoxide (DMSO) (80% DMSO and 20% distilled water). Preliminary studies to ascertain the influence of vehicle solution, in which all the title compounds were dissolved, showed no significant changes in seizure response.

The animals were also observed for their behavioral symptoms according to the Irwin scheme.[12] The anticonvulsant activity was evaluated by the maximal electroshock-induced seizure test (MES), using a modification of the method of Woodbury and Devenport.[13] Groups of 10 rats were employed. Maximal seizures were elicited by a 50-mA, 60-Hz alternating current, delivered through ear electrodes for 0.2 s, 60 min after drug administration. The failure to show tonic hind limb extension indicated protecting activity. The anticonvulsant properties of these derivatives were also evaluated in DBA/2 mice, which are genetically susceptible to sound-induced seizures. The mice were exposed 45 min after the administration of vehicle or pyrrolobenzimidazolone derivatives to a sound of mixed frequency and of 109-dB intensity for up to 60 s, which triggers a characteristic sequence of seizure–response in control DBA/2 mice, consisting of wild running, clonus tonus, and frequently respiratory arrest. The control and drug-treated mice were scored for latency to and incidence of the different phases of the seizures.[14] These results were compared with the activity showed by other clinically useful anticonvulsants such as diphenylhydantoin (Aldrich) and valproate (Sigma-Tau) (Table II). ED_{50} values were calculated by the method of Litchfield and Wilcoxon.[15]

Registry No. 1, 95-54-5; **2** (R″ = 4-ClC_6H_4), 3984-34-7; **2** (R″ = 4-FC_6H_4), 366-77-8; **3**, 15311-72-5; **4**, 39484-92-9; **5**, 116910-57-7; **6**, 116910-58-8; **7**, 115072-98-5; **8**, 115072-99-6; **9**, 115073-00-2; **10**, 115073-01-3; **11**, 115073-02-4; **12**, 115073-03-5; **13**, 115073-04-6; **14**, 115073-05-7; **15**, 115073-06-8; **16**, 115073-07-9; **17**, 115073-08-0; **18**, 115073-09-1.

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