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SYNTHESIS AND ANTICONVULSANT PROPERTIES OF NEW 1–PHENYL AND 1–PHENYLAMINO–3–PHENYLPYRROLIDINE–2,5–DIONE DERIVATIVES

JOLANTA OBNISKA, ALFRED ZEJC and AGNIESZKA ZAGÓRSKA

Department of Pharmaceutical Chemistry, Collegium Medicum
of the Jagiellonian University, 9 Medyczna Str., 30–688 Kraków, Poland

Abstract: A series of N–aryl and N–aminoaryl 3–phenyl pyrrolidine–2,5–diones were synthesized and tested for anticonvulsant activity in the maximum electroshock seizure (MES) and pentetrazol seizure threshold (sc Met) tests. Structures of the novel compounds were confirmed by elemental and spectral analyses.

Keywords: anticonvulsant activity, pyrrolidine–2,5–dione, succinimides.

In search for a new compounds with predictable anticonvulsant properties, our attention was drawn to a group of 3–phenylpyrrolidine–2,5–dione with different substituents at the nitrogen atom (1,2). Previous reports (3,4,5) showed the anticonvulsant activity of N–pyridyl–3–arylpyrrolidine–2,5–dione which displayed protection against MES. In addition, it was also reported that a significant effect on the activity of this compounds being exerted by the presence, position and characteristic of the substituents in pyridine moiety. Crystallographic investigations (6,7) showed that their pharmacological properties were connected with the conformation. The conformation of pharmacologically inactive molecules differs from that of molecules with a confirmed activity.

This report will provide further structure–activity studies on the 3–phenylpyrrolidine–2,5–diones in which pyridine moiety is replaced by the aryl ring with methyl or chloro substituents [comp. **I–VII**] or by the phenylamino or diphenylamino moiety [comp. **VIII–XI**].

The requirement for NH group linking the pyrrolidine–2,5–dione system to the aromatic ring was also investigated. Accordingly, a series of new N–aryl substituted 3–phenylpyrrolidine–2,5–diones, was synthesized and evaluated for anticonvulsant activity.

As the starting materials for the synthesis 3–(2–chlorophenyl)–, 3–(3–chlorophenyl)–, 3–(4–chlorophenyl)–,3–(3–fluorophenyl)–, 3–(3–bromophenyl)– and 3–phenylsuccinic acids synthesized by the method of Miller et al (8), as modified by Lange et al. (9) were used. The acids were cyclized to 1–phenyl or 1–phenylamino–3–phenylpyrrolidine–2,5–dione derivatives [**I–XI**] by heating them at ca. 190°–200°C for 1.5–2 h with appropriate arylamine (Scheme 1) or with arylhydrazine.

EXPERIMENTAL

Chemistry

Melting points (°C) were uncorrected, ^{1}H NMR spectra [**I –XI**] were recorded in $CDCl_3$ solution by using TMS as an internal standard (Bruker VM 250 MHz NMR Spectrometer). The chromatography was performed with Merck silica gel GF_{254} precoated TLC sheets using the following developing systems: A – chloroform: aceton (9:1), B – chloroform: methanol: acetic acid (60: 10: 5). Spots were detected by their absorption under UV light and visualization with 0.05 mol I_2 in 10% HCl.

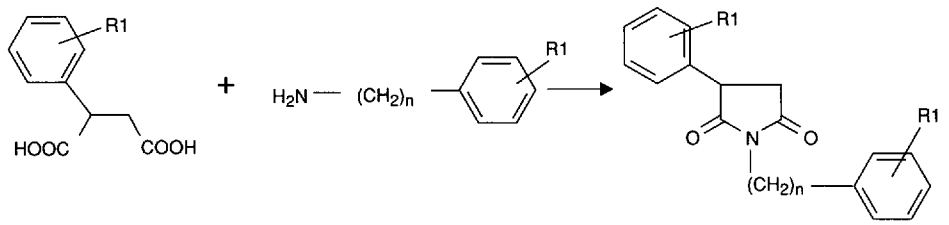
1–Phenyl and 1–phenylamino–3–phenylpyrrolidine–2,5–dione derivatives [**I – XI**].
General procedure.

An appropriate arylamine or arylhydrazine (0.02 mole) were dissolved in 25 ml of water and appropriate 2–substitute succinic acid (0.02 mole) was gradually added. The mixture was heated in oil bath with simultaneous distillation of water. After complete removal of water, the temperature of the reaction mixture was raised up to 190–200°C and maintained for 1.5 h. The crude product was recrystallized from ethanol.

Physicochemical data, ^{1}H NMR data, yields and elementary analysis results of the compounds synthesized were presented in Table 1a, b.

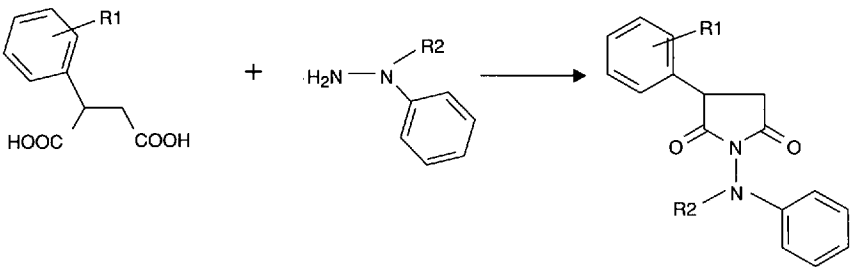
Pharmacology

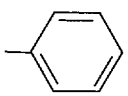
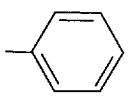
Compounds **I–XI** were pharmacologically pre–evaluated within the Antiepileptic Drug Development (ADD) Program, Epilepsy Branch, Neuro-



	I	II	III	IV	V	VI	VII
n	0	0	1	0	0	0	0
R1	–H	3–F	3–F	3–Cl	4–Cl	3–Br	3–Br
R2	2–CH_3	2–CH_3, 4–Cl	4–CH_3	4–CH_3	3–Cl	2–CH_3	4–CH_3

Scheme 1.



	VIII	IX	X	XI
R1	–H	2–Cl	4–Cl	4–Cl
R2		–H		–H

Scheme 2.

logical Disorders Program National Institutes of the Neurological and Communicative Disorders and Stroke (NINCDS), by using the testing procedures described elsewhere (10,11). Phase I studies involved three tests: maximum electroshock seizure (MES), subcutaneous pentylenetetrazole (sc Met), and the neurotoxicity (TOX). The MES test is a model for generalized tonic–clonic seizures. In this test, an electrical stimulus of 0.2 s in duration (50 mA in mice at 60 Hz) is delivered *via* corneal electrodes. Mice are tested for 30 min. and 4 h with the following doses: 30, 100, 300 mg/kg of test compound (12).

The scMet is a model for compounds that raise a seizure threshold. In scMet test a dose of metrazol is 85mg/kg in mice. This produces clonic seizures during a period of at least 5 seconds in 97% of tested animals. The metrazol is administrated subcutaneously. The test compounds are administrated intraperitoneally, suspended in 0.5% methylcellulose at the doses of 30, 100, 300 mg/kg (13). Neurotoxicity, induced by a test compound, is

Table 1a. Experimental data for compounds **I–VII**

No.	Molecular Formula Weight	Yield % Mp. [°C]	Analysis cal./found %C	%H	%N	^{1}H NMR/$CDCl_3$/δ	R_f/ solvent
I	$C_{17}H_{15}O_2N_1$ 265.3	73 120–122	77.05 76.93	5.75 5.66	5.28 5.38	2.53 (3H, s, CH_3), 2.75–2.90 (1H, d, imide), 3.35–3.42 (1H, q, imide), 4.08–4.40 (1H, q, imide), 7.10–7.60 (9H, m, arom)	0.67A 0.82B
II	$C_{17}H_{13}O_2N_1Cl_1F$ 317.74	50 104–105	64.21 64.27	4.12 4.07	4.40 4.26	2.15 and 2.19 (3H, 2 s, CH_3), 2.96–3.00 (1H, td, imide), 3.40–3.51 (1H, dq, imide), 4.20–4.32 (1H, q, imide), 6.99–7.40 (7H, m, arom)	0.80A 0.79B
III	$C_{18}H_{16}O_2N_1F$ 297.33	48 57–60	72.79 72.30	5.43 5.29	4.72 4.48	2.32 (3H, s, CH_3), 2.74–2.83 (1H, d, imide), 3.14–3.24 (1H, d, imide), 3.97–4.02 (1H, q, imide), 4.42–4.74 (2H, q, CH_2), 6.87–7.38 (8H, m, arom)	0.72A 0.84B
IV	$C_{17}H_{14}O_2N_1Cl$ 299.75	65 148–150	68.06 68.05	4.70 4.63	4.67 4.51	2.18 and 2.21 (H, 2s, CH_3), 2.97–3.04 (1H, td, imide), 3.38–3.50 (1H, dq, imide), 4.18–4.29 (1H, dq, imide), 7.08–7.45 (7H, m, arom)	0.78A 0.86B
V	$C_{16}H_{11}O_2N_1Cl_2$ 320.70	58 132–134	59.87 60.02	3.45 3.43	4.36 4.12	2.92–3.00 (1H, dd, imide), 3.33–3.42 (1H, q, imide), 4.15–4.20 (1H, q, imide), 7.23–7.49 (8H, m, arom)	0.82A 0.79B
VI	$C_{17}H_{14}O_2N_1Br$ 344.22	52 58–61	59.36 58.98	4.10 4.02	4.07 3.90	2.15–2.18 (3H, d, CH_3), 2.92–2.96 and 3.01–3.06 (1H, dt, imide), 3.33–3.48 (1H, dq, imide), 4.14–4.24 (1H, q, imide), 7.20–7.48 (8H, m, arom)	0.80A 0.85B
VII	$C_{17}H_{14}O_2N_1Br$ 344.22	50 62–64	59.36 59.13	4.10 4.14	4.07 3.72	2.15–2.18 (3H, 2s, CH_3), 2.92–3.05 (1H, dq, imide), 3.23–3.49 (1H, dq, imide), 4.14–4.24 (1H, dq, imide), 7.07–7.50 (8H, m, arom)	0.72A 0.83B

Table 1b. Experimental data for compounds **VIII–XI**

No.	Molecular Formula Weight	Yield % Mp. [°C]	Analysis cal./found %C	%H	%N	^{1}H NMR/$CDCl_3$/δ	R_f/ solvent
VIII	$C_{22}H_{18}O_2N_2$ 342.40	60 112–116	77.06 76.85	5.31 4.92	8.34 8.19	2.89–3.00 (1H, dd, CH_2imide), 3.24–3.39 (1H, dd, CH_2imide), 4.09–4.17 (1H, q, CH imide), 7.09–7.42 (15H, m, arom)	0.73A 0.84B
IX	$C_{16}H_{13}O_2N_2Cl$ 300.74	68 158–159	63.85 63.82	4.35 4.01	9.31 9.18	2.91–2.94 (1H, dd, CH_2imide), 3.27–3.41 (1H, dd, CH_2imide), 4.37–4.45 (1H, q, CH imide), 6.30 (1H, s NH), 6.85–7.45 (9H, m, arom)	0.84A 0.94B
X	$C_{22}H_{17}O_2N_2Cl$ 376.83	74 159–161	70.09 70.43	4.55 4.85	7.43 7.46	2.91–2.94 (1H, dd, CH_2imide), 3.27–3.41 (1H, dd, CH_2imide), 4.37–4.45 (1H, q, CH imide), 6.30 (1H, s NH), 6.85–7.45 (9H, m, arom)	0.79A 0.89B
XI	$C_{16}H_{13}O_2N_1Cl$ 300.74	65 173–174	63.85 64.28	4.35 4.31	9.31 8.81	2.90–3.03 (1H, m, imide), 3.26–3.35 (1H, m, imide), 4.34–4.42 (1H, m, imide), 6.69–6.80 (2H, m, arom), 7.13–7.51 (7H, m, arom), 8.44 (1H, s, NH)	0.69A 0.87B

Table 2a. Anticonvulsant Screening Project (ASP) Phase I Test results in mice (comp. **I–VII**)

Comp.	Dose	Activity				Tox[c]		ASP[d]
		MES[a]		sc Met[b]				
	mg/kg	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	class
I	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	1/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	4/5	0/1	0/4	0/2	
II	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
III	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	1/1	0/1	0/4	0/2	
IV	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
V	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	
VI	30	1/4	0/1	0/1	0/1	0/4	0/2	1
	100	3/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	1/1	0/1	0/4	0/2	
VII	30	0/1	0/1	0/1	0/1	0/4	0/2	1
	100	1/3	0/3	0/1	0/1	0/8	0/4	
	300	1/1	0/1	3/5	0/1	1/4	0/2	

* Tonic extension
[a]Maximal electroshock test (number of animals protected/number of animals tested)
[b]Subcutaneous pentylenetetrazole test
[c]Rotorod toxicity (number of animals exhibiting toxicity/number of animals tested)
[d]The classification is as follows:
1–anticonvulsant activity at doses 100 mg/kg or less
2–anticonvulsant activity at doses greater than 100 mg/kg
3–compound inactive at 300 mg/kg

Table 2b. Anticonvulsant Screening Project (ASP) Phase I Test results in mice (comp. **VIII–XI**)

Comp.	Dose	Activity				Tox[c]		ASP[d]
		MES[a]		sc Met[b]				
	mg/kg	0.5 h	4 h	0.5 h	4 h	0.5 h	4 h	class
VIII	30	0/1	0/1	0/1	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	1/5	0/1	0/2	0/2	
IX	30	0/1	0/1	0/1*	0/1	0/4	0/2	2
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	1/5	0/1	0/4	0/2	
X	30	0/1	0/1	0/1*	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	1/4	0/2	
XI	30	0/1	0/1	0/1	0/1	0/4	0/2	3
	100	0/3	0/3	0/1	0/1	0/8	0/4	
	300	0/1	0/1	0/1	0/1	0/4	0/2	

* Tonic extension
[a]Maximal electroshock test (number of animals protected/number of animals tested)
[b]Subcutaneous pentylenetetrazole test
[c]Rotorod toxicity (number of animals exhibiting toxicity/number of animals tested)
[d]The classification is as follows:
1–anticonvulsant activity at doses 100 mg/kg or less
2–anticonvulsant activity at doses greater than 100 mg/kg
3–compound inactive at 300 mg/kg

detected in mice using a rotorod test. Untreated control mice, when placed on a 6 r.p.m. rotation rod can maintain their equilibrium for a prolonged time. Neurotoxicity is indicated by the inability of a mouse maintaining equilibrium for one minute in each of the three successive trials (14). Results are given in Table 2a, b.

RESULTS

In a series of 1,3–diphenylpyrrolidine–2,5–diones [**I–VII**] compounds **I, III, VI,** and **VII** showed some anticonvulsant properties in phase I of screening project. The 1–(2–methylphenyl)–3–phenylpyrrolidine–2,5–dione **I** and three analogues of this compound **III, VI, VII** were found to be effective in this screening procedure. The most potent in MES test was 1–(2–methylphenyl)–3–(3–bromophenyl)pyrrolidine–2,5–dione **VI**, which protected all animals after 0.5 h at 30, 100 and 300 mg/kg. The 1–(4–methylphenyl)–3–(3–fluorophenyl)pyrrolidine–2,5–dione **III** had anticonvulsant properties but only at a dose of 300 mg/kg. This compounds in the scMet test at a dose of 300 mg/kg showed marginal anticonvulsant properties. Some activity was recorded in the scMet test also for compounds **I, VI, VII** (active at 300 mg/kg at 4h).

The presence and position of the methyl group in N–aryl moiety appears to be essential for the anticonvulsant activity in this group of compounds. The most potent in MES test were compounds with the methyl group in position 2 or 4 of the 1–phenyl ring *viz.*, **I, VI** and **VII**. The change of the brom atom for chlor substituents on the 3–phenyl ring in compounds **IV** and **V** made them inactive. This effect maybe is connected with lower lipophilicity. The methylene bridge in compound **III** decreased the activity. Introduction of the second substituents (–Cl) in the 4–position of the 1–phenyl ring led to an inactive compound **II.**

In a series of 1–phenylamino derivatives **X, XI** were devoid of anticonvulsant activity. Compounds **VIII, IX** were active only in the scMet test at 0.5 h using 300 mg/kg. This result suggests that the NH group, linking 1–phenyl ring with 3–phenylpyrrolidine–2,5–dione moiety, is probably not necessary for anticonvulsant activity.

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