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DRUG SYNTHESIS

SYNTHESIS OF NEW N–SUBSTITUTED CYCLIC IMIDES WITH AN EXPECTED ANXIOLYTIC ACTIVITY. XXII. DERIVATIVES OF 1–METHOXY–5–BICYCLO[2.2.2]–OCT–5–ONE–2,3–DICARBOXIMIDE

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Abstract: Continuing our studies with the design of new anxiolytics we have now synthesized a series of new compounds, derivatives of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide bearing a 4–aryl–1–piperazinylbutyl group attached to the imide nitrogen.

Keywords: derivatives of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide; synthesis; anxiolytic, antidepressive activity

It has been reported that many selective ligands of serotonin 5–HT_{1A} receptors, structural analogs of buspirone (Figure 1, Figure 2), display an anxiolytic activity (tandospirone, gepirone, ipsapirone and others) (1–3).

Previously synthesized derivatives of N–(4–substituted–1–piperazinylalkyl)imides displayed an expected affinity to 5–HT_{1A} receptors and anxiolytic activity in behavioral tests (4–9). Regarding that, and having in mind the very promising anxiolytic and antidepressive activity of previously obtained N–[4(4–methoxyphenyl–1–piperazinyl)butyl]–1–ethoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide (10) we have designed and carried out the synthesis and biological evaluation of a series of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide (Figure 3).

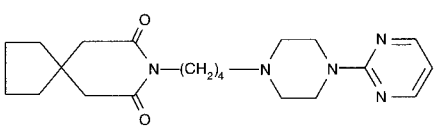


Figure 1. Buspirone

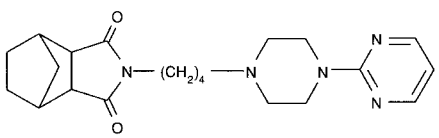


Figure 2. Tandospirone

The initial compound for our syntheses was 3–methoxycyclohex–2–en–1–one. This compound was condensed with maleimide in the presence of *p*–toluenosulfonic acid (catalytic quantities) in isopropenyl acetate. In this reaction 3–methoxycyclohex–2–en–1–one was converted to 1–methoxy–3–acetoxy–1,3–cyclohexadiene, which then served as the diene participant in Diels–Alder reaction with maleimide. The mixture of adducts **1** and **1A** resulting from this reaction was hydrolyzed by heating with aqueous–ethanolic solution of ammonia to give compound **1** (Scheme 1).

Compound **1** was alkylated with 1–bromo–4–chlorobutane or 1,3–dibromopropane in 2–butanone/anhydrous potassium carbonate to give 4–chlorobutyl (**2**) and 3–bromopropyl (**3**) derivatives. Compounds **2** and **3** were condensed with various 4–aryl– and 4–heteroaryl piperazines in appropriate solvents, in the presence of anhydrous potassium carbonate to yield compounds **4–15**

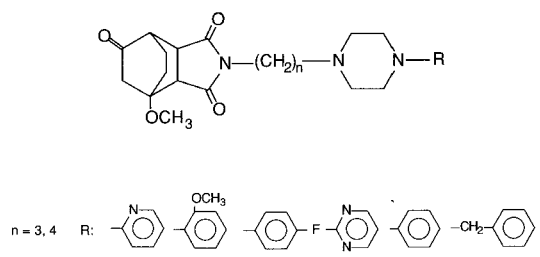
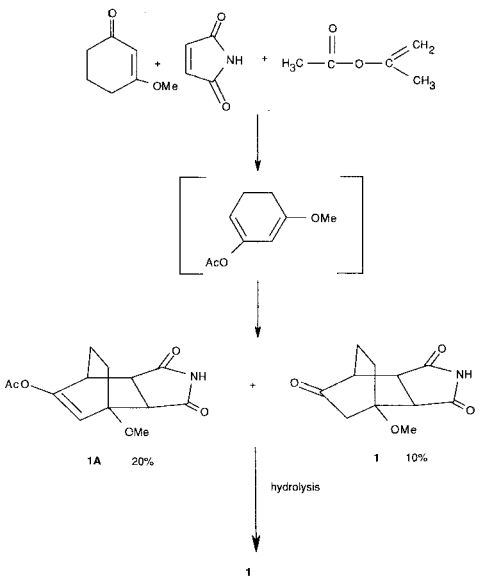


Figure 3. Our compounds



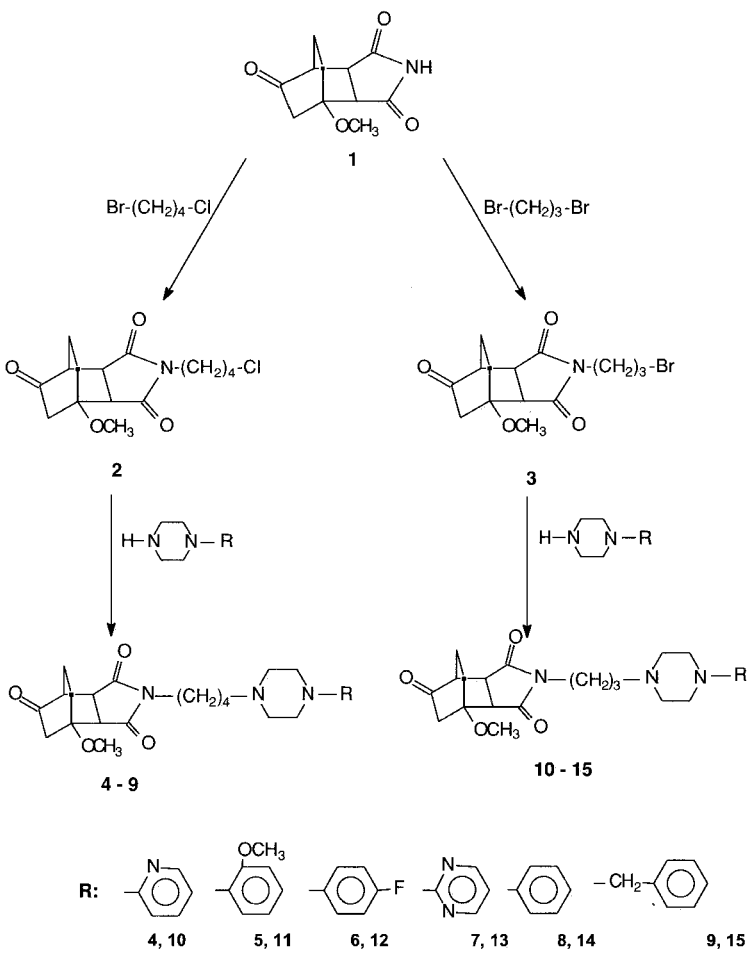
Scheme 1. Synthesis of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide.

(Scheme 2). Compounds **1–15** are described in Table 1. The new compounds were characterized by ^{1}H NMR and IR spectra and elemental analysis (Table 1).

EXPERIMENTAL

Pharmacology

In several studies it was shown that addition of a 2–methoxy group to the phenyl part of the discussed compounds increases 5–HT_{1A} receptor affinity, also replacement of the benzene ring with pyrimidine raises 5–HT_{1A} receptor affinity (11,12). Considering that we selected two compounds containing 1–(2–pyrimidynyl)–piperazinylbutyl and 1–(*o*–methoxyphenyl)–piperazinylbutyl spacers for pharmacological tests. The hydrochlorides of compounds **5** and **7** were tested for CNS activity in the Institute of Psychiatry and Neurology in Warsaw (headed by Prof. dr hab. W. Kostowski). These compounds were submitted to general (Open Field



Scheme 2. Synthesis of derivatives of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide.

Table 1. Physical, analytical and ^{1}H NMR spectral data of compounds **1–15**.

Comp. No.	Formula Molecular weight	Solvent m.p. [°C]	Yield [%]	Analysis Calculated/Found %C	%H	%N	^{1}H NMR, δ (ppm) $CDCl_3$
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	$C_{11}H_{13}NO_4$ 223.22	ethyl acetate 216–217	70	59.19 58.95	5.83 5.97	6.27 5.99	8.24 (br.s, 1H, NH), 3.42 (s, 3H, $-OCH_3$), 3.55 (dd, J_1=9.6 Hz, J_2=2.2 Hz, 1H, C2–H), 3.23, (dd, J_1=10 Hz, J_2=3.2 Hz, 1H, C3–H), 2.86 (m, 1H, C4–H), 2.46 (m, 2H, C6–H), 2.01 (m, 3H, C8–H), 1.80 (m, 1H, C7–H).
2	$C_{15}H_{20}NO_4Cl$ ·0.25 H_2O 317.96	hexane/ benzene 81–82	81	56.65 56.90	6.49 6.27	4.41 4.41	3.53 (m, 4H, C1'–2H, C4'–2H), 3.44 (s, 3H, $-OCH_3$), 3.31 (dd, J_1=9.6 Hz, J_2=2.2 Hz, 1H, C3–H), 3.18 (dd, J_1=9.8 Hz, J_2=3Hz,1H, C2–H), 2.86 (m, 1H, C4–H), 2.53 (dd, J_1=18.9 Hz, J_2=2.2 Hz, 1H, C6–H_a), 2.21 (dd, J_1=19.4 Hz, J_2=2.4 Hz, 1H, C6–H_b), 2.14–1.77 (m, 4H, C7–H, C8–H), 1.76 (m, 4H, C3'–H, C4'–H).
3	$C_{14}H_{18}NO_4Br$ 344.19	hexane/ benzene 89–91	75	48.85 49.12	5.27 5.69	4.07 4.34	3.64 (t of d, J_1=6.6 Hz, J_2=2 Hz, 2H, C1'–H), 3.44 (s, 3H, C1–OCH_3), 3.32 (m, 3H, C3'–H, C3–H), 3.19 (dd, J_1=9.8 Hz, J_2=3 Hz, 1H, C2–H), 2.87 (m, 1H, C4–H) 2.54 (dd, J_1=18.9 Hz, J_2=2.2 Hz, 1H, C6–H_a), 2.21 (dd, J_1=19.6 Hz, J_2=2.6 Hz, 1H, C6–H_b), 2.17–1.73 (m, 6H, C7–H, C8–H, C2'–H).
4	$C_{24}H_{32}N_4O_4$ 440.54	hexane/ benzene 91–93	69	65.43 65.78	7.32 7.46	12.76 12.91	8.18 (m, 1H, H_α–pyr), 7.48 (m, 1H, H_γ–pyr), 6.62 (m, 2H, H_β–pyr), 3.56 (m, 6H, C1'–H, $(CH_2)_2$–N–Pyr), 3.44 (s, 3H, $-OCH_3$), 3.31 (dd, J_1=9.6 Hz, J_2=2 Hz, 1H, C3–H), 3.18 (dd, J_1=9.6 Hz, J_2=3.2 Hz, 1H, C2–H), 2.87 (d, J=3 Hz, 1H, C4–H), 2.60 (m, 4H, $N(CH_2)_2$), 2.47 (m, 2H, C4'–H), 2.28–1.95(m, 4H, C6, C7–H), 1.84–1.56 (m, 6H, C8–H, C2'–H, C3'–H).
5	$C_{26}H_{35}N_3O_5$ 469.57	hexane/ benzene 122–123	76	66.49 66.58	7.51 7.56	8.95 8.89	6.94 (m, 4H, H_{arom}), 3.86 (s, 3H, $-OCH_3\varphi$), 3.52 (t, J=6.8 Hz, 2H,C1'–H), 3.44 (s, 3H, $-OCH_3$), 3.29 (dd, J_1=9.8 Hz, J_2=2 Hz, 1H, C3–H), 3.15 (m, 5H, C2–H, $(CH_2)_2N-\varphi$), 2.88 (m, 1H, C4–H), 2.65 (m, 4H, N–$(CH_2)_2$), 2.58–2.39 (m, 3H, C4'–H, C6–H_a), 2.23 (dd, J_1=19.4 Hz, J_2=2.2 Hz, 1H, C6–H_b), 2.19–1.76 (m, 4H, C7–H, C8–H), 1.53 (m, 4H, C2'–H, C3'–H).

Table 1. continued

Comp. No.	Formula Molecular weight	Solvent m.p. [°C]	Yield [%]	Analysis Calculated/Found %C	%H	%N	^{1}H NMR, δ (ppm) $CDCl_3$
1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
6	$C_{25}H_{32}N_3O_4F$ 457.54	hexane/ benzene 97–99	66	65.62 65.33	7.05 6.90	9.18 9.02	7.15–6.84 (m, 4H, H_{arom}), 3.52 (t, J=6.5 Hz, 2H, C1'–H), 3.45 (s, 3H, $-OCH_3$), 3.30 (dd, J_1=9.6 Hz, J_2=2 Hz, 1H, C3–H), 3.18 (m, 5H, C2–H, $(CH_2)_2$–NΦ), 2.87 (m, 1H, C4–H), 2.69–2.48 (m, 6H, C4'–H, $N(CH_2)_2$), 2.23 (dd, J_1=19.4 Hz, J_2=2.2 Hz, 1H, C6–H_a), 2.03 (m, 3H, C6–H_b, C7–H), 1.84–1.55 (m, 6H, C8–H, C2'–H, C3'–H).
7	$C_{23}H_{31}N_5O_4$ 441.53	hexane/ benzene 72–74	62	62.56 62.44	7.08 7.13	15.86 15.68	8.30 (d, J=4.6 Hz, 2H, H_γ–pyr), 6.47 (dd, J_1=4.8 Hz, J_2=4.8 Hz, 1H, H_β–pyr), 3.84 (m, 4H, $(CH_2)_2$N–Pyr), 3.51(m, 2H, C1'–H), 3.44 (s, 3H, $-OCH_3$), 3.29 (dd, J_1=9.8 Hz, J_2=2 Hz, 1H, C3–H), 3.16 (dd, J_1=9.8 Hz, J_2=3.2 Hz, 1H, C2–H), 2.87 (m, 1H, C4–H), 2.48 (m, 4H, $(CH_2)_2$N), 2.39 (t, J=7 Hz, 2H, C4'–H).
8	$C_{25}H_{33}N_3O_4$ 439.55	hexane/ benzene 88–90	63	68.30 68.21	7.56 7.48	9.56 9.34	7.26 (m, 2H, H_{arom}), 6.88 (m, 3H, H_{arom}), 3.52 (t, J=6.8 Hz, 2H, C1'–H), 3.44 (s, 3H, $-OCH_3$), 3.28 (dd, J_1=9.8 Hz, J_2=2 Hz, 1H, C3–H), 3.18 (m, 5H, C2–H, $(CH_2)_2$–Nφ), 2.88 (m, 1H, C4–H), 2.60 (m, 4H, $N(CH_2)_2$), 2.40 (t, J=7 Hz, 2H, C4'–H), 2.23 (dd, J_1=19.2 Hz,J_2=2.6 Hz, 1H, C6–H_a), 2.04 (m, 3H, C6–H_b, C7–H), 1.80 (m, 2H, C8–H), 1.53 (m, 4H, C2'–H, C3'–H).
9	$C_{27}H_{35}N_3O_4$ 453.57	hexane/ benzene 65–67	58	68.84 68.57	7.77 7.71	9.26 8.94	7.28 (m, 5H, H_{arom}), 3.50 (m, 2H, C1'–H), 3.44 (s, 3H, $-OCH_3$), 3.27 (dd, J_1=9.6 Hz, J_2=2.2 Hz, 1H, C3–H), 3.14 (dd, J_1=9.8 Hz, J_2=3.4 Hz, 1H, C2–H), 2.86 (m, 1H, C4–H), 2.46 (m, 10H, piperazine–H, benzyl–H), 2.32 (m, 3H, C4'–H, C6–H_a), 2.01 (m, 3H, C6–H_b, C7–H), 1.83–1.67 (m, 2H, C8–H), 1.47 (m, 4H, C2'–H, C3'–H).
10	$C_{23}H_{30}N_4O_4$ 426.47	heksane/ benzene 138–141	80	64.77 64.66	7.09 6.92	13.13 13.22	8.18 (m, 1H, H_α–pyr), 7.47 (m, 1H, H_γ–pyr), 6.62 (m, 2H, H_β–pyr), 3.55 (m, 6H, C1'–H, $(CH_2)_2$N–Pyr), 3.44 (s, 3H, $-OCH_3$), 3.27 (dd, J_1=9.4 Hz, J_2=2.4 Hz, 1H, C3–H), 3.15 (dd, J_1=9.8 Hz, J_2=3.2 Hz, 1H, C2–H), 2.88 (m, 1H, C4–H), 2.52 (m, 5H, C6–H_a, N–$(CH_2)_2$), 2.37 (t, J=7.2 Hz, 2H, C3'–H), 2.29–2.18 (m, 1H, C6–H_b), 2.10–1.67 (m, 6H, C7–H, C8–H, C2'–H).

Table 1. continued

Comp. No.	Formula Molecular weight	Solvent m.p. [°C]	Yield [%]	Analysis Calculated/Found %C	%H	%N	^{1}H NMR, δ (ppm) $CDCl_3$
1	2	3	4	5	6	7	8
11	$C_{25}H_{33}N_3O_5$ *2 HCl 528.56	metha-nol/ ether 226–227	77	56.80 57.07	6.67 6.63	7.95 7.98	12.50 (br.s, 1H, –NH), 7.11 (m, 2H, H_{arom}), 6.93 (m, 2H, H_{arom}), 3.89 (s, 3H, φ–OCH_3), 3.63–3.39 [m, 10H, C1'–H, $(CH_2)_2$N–φ, N$(CH_2)_2$], 3.45 (s, 3H, –OCH_3), 3.25–2.85 (m, 5H, C3'–H, C3–H, C2–H, C4–H), 2.61–1.55 (8H, C6–H, C2'–H, C7–H, C8–H).
12	$C_{24}H_{30}N_3O_4F$ 443.48	hexane/ benzene 58–59	59	64.99 64.87	6.82 6.93	9.47 9.29	6.90 (m, 4H, H_{arom}), 3.58 (t, J=7.3 Hz, 2H, C1'–H), 3.44 (s, 3H, –OCH_3), 3.28 (dd, J_1=9.6 Hz, J_2=2.4 Hz, 1H, C3–H), 3.13 (m, 5H, C2–H, $(CH_2)_2$–Nφ), 2.87 (m, 1H, C4–H), 2.58–2.48 (m, 5H, $(CH_2)_2$N), 2.39 (m, 2H, C3'–H), 2.23 (m, 1H, C6–H_b), 2.02–1.67 (m, 6H, C7–H, C8–H, C2'–H).
13	$C_{22}H_{29}N_5O_4$ 427.50	hexane/ benzene 150–151	63	61.80 61.70	6.83 6.91	16.38 16.30	8.30 (d, J=4.8 Hz, 2H, H_{γ}-pyr), 6.47 (t, J_1=4.8 Hz, J_2=4.8 Hz, 1H, H_{β}-pyr), 3.80 (t, J=5.2 Hz, 4H, $(CH_2)_2$N– Pyr), 3.58 (t, J=7.2 Hz, 2H, C1'–H), 3.44 (s, 3H, C1–OCH_3), 3.28 (dd, J_1=9.6 Hz, J_2=2.2 Hz, 1H, C3–H), 3.15 (dd, J_1=9.8 Hz, J_2=3.4 Hz, 1H, C2–H), 2.87 (m, 1H, C4–H), 2.51 (m, 5H, C6–H_a, N$(CH_2)_2$), 2.35 (t, J=7.2Hz, 2H, C3'–H), 2.24 (dd, J_1=19.2 Hz, J_2=2.4 Hz, 1H, C6–H_b), 2.09–1.70 (m, 6H, C7–H, C8–H, C2'–H).
14	$C_{24}H_{31}N_3O_4$ 425.49	hexane/ benzene 105–108	74	67.74 67.69	7.34 7.29	9.87 9.51	7.27 (m, 2H, H_{arom}), 6.88 (m, 3H, H_{arom}), 3.58 (t, J=7.3 Hz, 2H, C1'–H), 3.44 (s, 3H, –OCH_3), 3.27 (dd, J_1=9.4 Hz, J_2=2.2 Hz, 1H, C3–H), 3.18 (m, 5H, C2–H, $(CH_2)_2$–Nφ), 2.86 (m, 1H, C4–H), 2.56 (m, 4H, N$(CH_2)_2$), 2.37 (t, J=7.1 Hz, 2H, C3'–H), 2.24 (dd, J_1=19.6 Hz, J_2=2.2 Hz, 1H, C6–H_a), 2.02 (m, 3H, C6–H_b, C7–H), 1.76 (m, 4H, C8–H, C2'–H).
15	$C_{25}H_{33}N_3O_4$ 439.51	hexane/ benzene 102–103	61	68.31 68.02	7.56 7.29	9.56 9.36	7.30 (m, 5H, H_{arom}), 3.53 (m, 4H, C1'–H, NCH_2–φ), 3.43 (s, 3H, –OCH_3), 3.22 (dd, J_1=9.8 Hz, J_2=2 Hz, 1H, C3–H), 3.10 (dd, J_1=9.8 Hz, J_2=3.4 Hz, 1H, C2–H), 2.84 (m, 1H, C4–H), 2.56–2.16 (m, 11H, $(CH_2)_2$N–CH_2φ, C6–H_a), 1.99 (m, 3H, C6–H_b, C7–H), 1.73 (m, 4H, C8–H, C2'–H).

Test) and antidepressive (Porsolt Test) activity tests. Male Wistar rats weighing 200–250 g were used in all experiments. They were brought into the laboratory 1 week before experimental and were housed in groups of 10–12 with free access to food and water.

Open Field Test (13). Compounds **5** and **7** were injected intraperitoneally at a dose level of 1 mg/kg in a 0.1 ml/100g body weight volume before testing. 0.9% NaCl was injected to the control group of rats. The apparatus consisted of a round arena box, 80 cm in diameter, 3 photosensors and a recording system. The animals were not maintained before the experiment. The behavior of animals was assessed for 10 min and recorded on a videotape. The locomotor activity analysis was subsequently performed from the recording, and the following parameters were recorded: general activity (number of photobeam interruptions), number of entries into the central part of the open field and time of stay in the central part.

Porsolt Test (14,15). On the first day, the rats were placed individually for 15 min into a glass cylinder (height 40 cm, diameter 18 cm) containing 16 cm of water, maintained at 25°C. On the second day, the animals were treated 60 min before water immersion. Compounds **5** and **7** were injected intraperitoneally at a dose level of 1 mg/kg and 5 mg/kg in a 0.1 ml/100 g body weight volume before testing. 0.9% NaCl was injected to the control group of rats. The duration of mobility during the 5–min testing period was recorded. A rat was considered to be mobile when it tried to make apparent attempts to escape from the cylinder.

The obtained data were analyzed by ANOVA followed by Mann–Whitney test.

RESULTS AND DISCUSSION

Compounds **5** and **7** exhibited a very weak anxiolytic activity. Antidepressive activity was not observed. In the Open Field Test these compounds insignificantly increased the spontaneous locomotor activity and the number of enters on the central sector of field. The data are shown in Table 2.

In the Porsolt Test, compound **7** showed a tendency for inhibiton of rats' activity that may be the result of its sedative properties, although one cannot exclude another mechanism of action. The data are shown in Figure 4.

Chemistry

Melting points were determined in a capillary Kofler's apparatus and are uncorrected. IR spectra were recorded using a Specord 75 IR spectrophotometer (Zeiss, Jena) in KBr pellets; ^{1}H NMR spectra were recorded using a Varian UNITY-plus–200 spectrometer, operating at 199.97 MHz for ^{1}H. The chemical shift values [ppm] were referenced downfield to TMS at ambient temperature. The results of elemental analyses (C, H, N) were within ± 0.5 % of theoretical values. The IR spectra of the compounds showed absorption bands at 1688 cm^{-1} – 1740 cm^{-1} indicating the presence of multiple C=O groups.

SYNTHESIS OF 1–METHOXYBICYCLO[2.2.2]–OCT–5–ONE–2,3–DICARBOXIMIDE [**1**]

3–methoxycyclohex–2–en–1–one (0.039 mole; 5.0 g), maleimide (0.039 mole; 4.2 g) and 50 mg of *p*–toluenesulfonic acid were refluxed for 20 h with 30 ml of isopropenyl acetate. The solvent was removed on a rotary evaporator. The residue was crystallized from ethyl acetate. In this reaction we obtained two compounds. The mixture of these

Table 2. The effect of compounds **5** and **7** on rats' behavior in the Open Fields Test. The data are shown as mean ± SEM. The number of rats in the groups varied from 10 to 12, * = P related to control group (saline).

Comp. dose (mg/kg)	Activity	Central entries	Time in central sector
Saline	2424 ± 264	4.75 ± 1.21	67 ± 18.7
5			
1 mg/kg	1977 ± 352	3.00 ± 1.32	82 ± 40.3
5 mg/kg	1179 ± 257	1.25 ± 0.42	174 ± 79.0
	$^{**}P< 0.01$	$^{**}P< 0.01$	
7			
1 mg/kg	2302 ± 406	2.14 ± 0.88	64 ± 26.7
5 mg/kg	1717 ± 386	1.57 ± 0.99	36 ± 24.4
		$^{*}P< 0.05$	$^{*}P< 0.05$

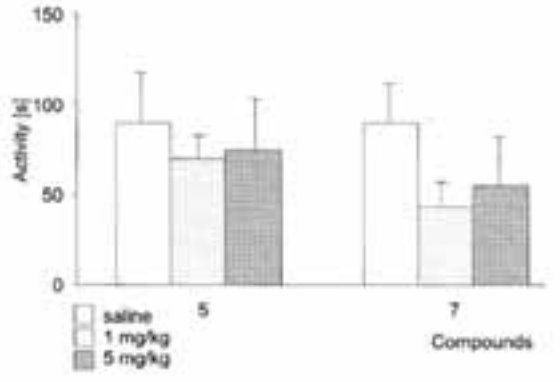


Figure 4. The effect of compounds **5** and **7** on rats' behavior in the Porsolt Test. The number of rats in the groups varied from 10 to 12. The data are shown as mean ±SEM. * = $P< 0.05$ related to control group (saline).

compounds was refluxed in ethanol and 30% ammonia for 1 h. The residue was crystallized from ethyl acetate to give compound **1**.

GENERAL METHOD OF PREPARING N–(4–CHLOROBUTYL)– OR (3–BROMOPROPYL)–1–METHOXYBICYCLO[2.2.2]–OCT–5–ONE–2,3–DICARBOXIMIDE **2** AND **3**

A mixture of 0.03 mole (6.7 g) of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide (**1**) and 0.07 mole (12.2g) of 1–bromo–4–chlorobutane or 0.18 mole (36.17 g) of 1,3–dibromopropane in 80 ml of ethylmethylketone was refluxed in the presence of 8 g of anhydrous K_2CO_3 for 58 h. The hot mixture was filtered and the solvent was removed on a rotary evaporator. The residue was crystallized from hexane to give compounds **2** or **3**.

GENERAL METHOD OF PREPARING N–[4(4–ARYL–1–PIPERAZINYL)BUTYL]–1–METHOXY–BICYCLO–[2.2.2]–OCT–5–ONE–2,3–DICARBOXIMIDE (**4–9**) AND N–[3(4–ARYL–1–PIPERAZINYL)–PROPYL]–1–METHOXYBICYCLO–[2.2.2]–OCT–5–ONE–2,3–DICARBOXIMIDE (**10–15**)

Compound **2** or **3** (0.03 mole), 0.03 mole of the appropriate amine, 1 g of anhydrous K_2CO_3 and 0.2 g of KI in 50 ml of ethylmethylketone were refluxed for 55 h. The hot mixture was filtered, and the solvent was removed on a rotary evaporator. The residue was crystallized from an appropriate solvent to yield compounds **4–15**.

CONCLUSIONS

This study is a continuation of our research regarding cyclic imides with potential anxiolytic and antidepressive (9,16) activity. In this paper we have described new derivatives of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide. According to our studies, we have selected two compounds (**5** and **7**) for pharmacological tests with theoretically the best anxiolytic and antidepressive activity. Compounds **5** and **7** showed a weak anxiolytic activity but antidepressive activity was not observed. Compound **7** showed sedative properties. The obtained results showed that the tested derivatives of 1–methoxybicyclo[2.2.2]–oct–5–one–2,3–dicarboximide showed a pharmacological activity.

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