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SYNTHESIS OF NEW *N*–SUBSTITUTED CYCLIC IMIDES WITH AN EXPECTED ANXIOLYTIC ACTIVITY. XVI. DERIVATIVES OF 1–ACETOXY–7,7–DIMETHYL–BICYCLO[2.2.2]OCTAN–5–ONE–2,3–DICARBOXIMIDE

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Abstract: The preparation of a potential anxiety–relieving compounds *N*–[4–(4–aryl)–1–piperazinyl)butyl]–1–acetoxy–7,7–dimethyl–bicyclo[2.2.2]octan–5–one–2,3–dicarboxmidies has been described. *N*–[4–(4–2–methoxyphenyl)–1–piperazinyl)butyl]–1–acetoxy–7,7–dimethyl–bicyclo[2.2.2]octan–5–one–2,3–dicarboximide **III** showed a strong sedative effect in Writh's test.

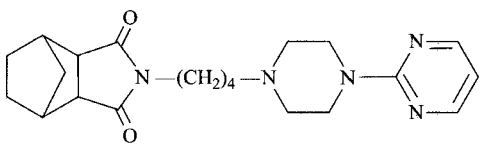
Keywords: 1–acetoxy–7,7–dimethyl–bicyclo[2.2.2]octan–5–one–2,3–dicarboximide derivatives, sedative effect

Many compounds of arylpiperazine group possess high affinity and selectivity for 5–HT_{1A} receptors (e.g. buspirone, gepirone, tandospirone, NAN–190, BMY7378) and have been applied as anxiolytic and antidepressive drugs (1,2). As a continuation of our studies on potential anxiety–relieving agents (3–9) a series of new products – derivatives of 1–acetoxy–5–keto–7,7–dimethyl–bicyclo[2.2.2]octane–2,3–dicarboximide has been designed.

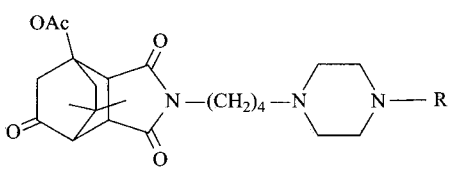
The aim of the present study was the synthesis of a series of compounds **III–IX** and the pharmacological profile of *N*–[4–(4–2–methoxyphenyl)–)–1–piperazinyl)butyl]–1–acetoxy–7,7–dimethylbicyclo [2.2.2]octan–5–one–2,3–dicarboximide **III**, selected as a representative. The design of these compounds was inspired in the structure of tandospirone (Figure 1). The spacers – N–butyl, N'–arylpiperazine groups used are supposed to introduce the desired CNS activity.

The first step of the synthesis of compounds **III–IX** was the preparation of 1,5–diacetoxy–7,7–dimethylbicyclo[2.2.2]oct–5–ene–2,3–dicarboximide (**I**) in the reaction of dimedone (5,5–dimethyl–1,3–cyclohexanedione), maleimide and isopropenyl acetate in the presence of *p*–toluenesulfonic acid. The reaction of imide **I** with the alkylating agent 1–bromo–4–chlorobutane was carried out in the presence of anhydrous potassium carbonate in 2–butanone. We found that the O–acetyl group was removed and enol–keto rearrangement occurred under these conditions. 5–keto–*N*–alkylated imide **II** was the only identified product. To complete the synthesis, compound **II** was condensed with appropriately N–substituted piperazines to give compounds **III–IX** (Scheme 1).

Compound **III** was classified as a derivative with an expected activity on 5–HT_{1A} receptor function. The profile of action of compound **III·2HCl** was determined by 5–HT_{1A} agonist–induced behavioral syndrome in the rat (flat body posture (FBP) and lower lip retraction (LLR) (10,11), neuroleptic (Writh's) test (12), conflict (Vogel) test (13) and antidepressive (Porsolt) test (14). Dopamine receptor function was assessed by measuring spontaneous open field locomotor activity (15).



Tandospirone



III - IX

Figure 1. The structures of tandospirone and the compounds **III–IX**.

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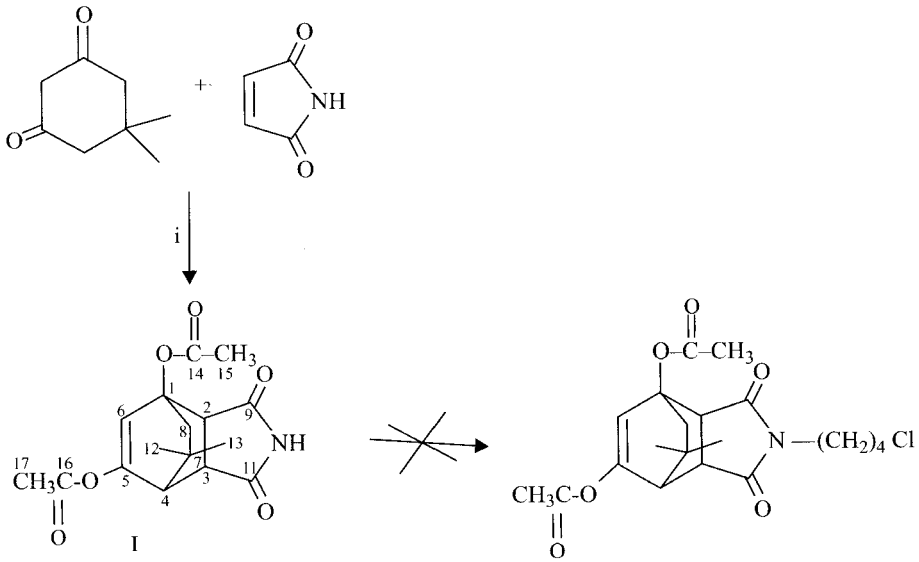

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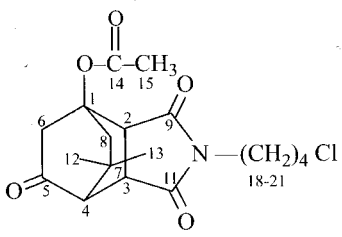
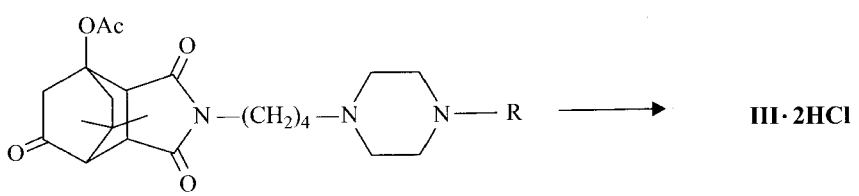


II

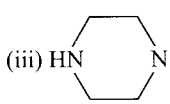
	R
III	2 -MeOPh
IV	Ph
V	Me
VI	4 - FPh
VII	$PhCH_2$
VIII	2 - pyridyl
IX	2 - pyrimidynyl



III - IX

Reagents: (i) p-TsOH, isopropenyl acetate, reflux

(ii) $Br(CH_2)_4Cl$, K_2CO_3, 2-butanone, reflux

(iii)  R, K_2CO_3, KI, 2-butanone, reflux

Scheme 1.

EXPERIMENTAL

Melting points were determined in a capillary Kofler apparatus and are uncorrected. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian UNITYplus–200 spectrometer, operating at 199.97 MHz for ^1H and at 50.28 MHz for ^{13}C. The chemical shift values, expressed in ppm, were referenced downfield to TMS at ambient temperature. IR spectra [KBr, cm^{-1}] were recorded on a Specord 75 IR spectrophotometer. Microanalyses were performed at the Warsaw Technical University Microanalysis Laboratory. Results obtained are within ± 0.4% of the calculated values.

1,5–diacetoxy–7,7–dimethylbicyclo[2.2.2]oct–5–ene–2,3–dicarboximide (I).

A mixture of dimedone (5,5–dimethyl–1,3–cyclohexanedione) (5 g, 36 mmole), maleimide (4.37 g, 45 mmole), *p*–toluenesulfonic acid (100 mg) and isopropenyl acetate (20 ml) was refluxed for 25 h. The solvent was evaporated and the residue was crystallized from benzene–hexane, m.p. 211–213°C. Yield 3.1 g (29%).

$C_{16}H_{19}NO_6$ (321.32)

IR (KBr) cm^{-1} 1779, 1760, 1710 (C=O); ^1H NMR ($CDCl_3$) δ 8.42 (br.s, 1H, NH), 5.91 (d, J=2.;0 Hz, 1H, H–6); 3.97 (d, J=8.4 Hz, 1H, H–2); 3.32 (dd, J_1=8.4 Hz, J_2=3.4 Hz, 1H, H–3); 2.56 (dd, J_1=3.4 Hz, J_2=2.0 Hz, 1H, H–4); 2.25 (d, J=12.2 Hz, 1H, H–8); 2.14, 2.13 (s, 2×3H, H–15, H–17); 1.52 (d, J=12.2 Hz, 1H, H–8); 1.16, 1.04 (s, 2×3H, H–12, H–13) ppm.

^{13}C NMR ($CDCl_3$) δ 178.02 (C11), 175.32 (C9), 170.63 (C14), 167.55 (C16), 148.17 (C5), 113.23 (C6), 81.01 (C1), 46.38 (C2), 44.13 (C8), 44.21 (C3), 42.69 (C4), 35.24 (C7), 30.45 (C127), 28.57 (C13), 22.09, 21.30 (C15, 17) ppm.

N–(4–chlorobutyl)–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximide (II).

A mixture of imide **I** (2.1 g, 6.53 mmole) and 1–bromo–4–chlorobutane (1.2 g, 6.9 mmole) and anhydrous K_2CO_3 (2.1 g, 15.1 mmole) in 2–butanone (55 ml) was refluxed for 24 h. The inorganic precipitate was filtered off and the solvent was evaporated. Compound **II** was crystallized from octane, m.p. 134–135°C. Yield 1.7 g (70%).

$C_{18}H_{24}NClO_5$ (369.88)

IR (KBr) cm^{-1} 1750, 1700–1650 (C=O); ^1H NMR ($CDCl_3$) δ 4.19 (dd, J_1=9.5 Hz, J_2=2.5 Hz, 1H, H–2); 3.57–3.48 (m, 4H, H–18, H–21); 3.41 (dd, J_1=9.9 Hz, J_2=3.5 Hz, 1H, H–3); 2.63 (dd, J_1=14.4 Hz; J_2=2.2 Hz, 1H, H–8); 2.54 (m, 2H, H–4–H–6); 2.23 (dd, J_1=19.5 Hz; J_2=3.2 Hz, 1H, H–6); 2.12 (s, 3H, H–15); 1.71 (m, 5H, H–8, H–19, H–20); 1.22, 1.06, s (2×3H, H–12, H–13) ppm.

^{13}C NMR ($CDCl_3$) δ 205.68 (C5), 176.35 (C9), 174.78 (C11), 170.69 (C14), 78.39 (C1), 55.35 (C4), 45.04 (C21), 44.05 (C6), 43.98 (C8), 41.44 (C2), 39.45 (C3), 38.18 (C18), 31.87 (C7), 31.06 (C12), 29.59 (C20), 28.90 (C13), 25.06 (C19), 22.08 (C15) ppm.

Preparing of N–[4–[4–(aryl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximides (III–IX)

A mixture of compound **II** (2 mmole), anhydrous K_2CO_3 (1 g, 7.2 mmole), KI (0.2 g, 1 mmole) and N–(aryl)piperazine (2 mmole), was refluxed in 2–butanone (50 ml). When the reaction was complete by TLC (silica gel, developing system: hexane–ethyl acetate) the mixture was filtered and the solvent was evaporated. The residue was crystallized from appropriate solvent.

N–[4–[4–(2–methoxyphenyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximide (III): m.p. 162–164°C (hexane). Yield 0.63 g (60%).

$C_{29}H_{39}N_3O_6$ (525.65)

IR (KBr) cm^{-1} 1710, 1680 (C=O); ^1H NMR ($CDCl_3$) δ 7.40–6.83 (m, 4H, ArH); 4.14 (dd, J_1=9.8 Hz, J_2=2.0 Hz, 1H, H–2); 3.86 (s, 3H, $ArOCH_3$); 3.50 (t, J=6.8 Hz, 2H, H–18); 3.40 (dd, J_1=9.8 Hz, J_2=3.4 Hz, 1H, H–3); 3.09 (m, 4H, piperazine); 2.68–2.50 (m, 4H, piperazine); 2.53 (d, J=3.4 Hz, 1H, H–4); 2.40 (t, J=7.1 Hz, 2H, H–21); 2.24 (dd, J_1=19.4 Hz; J_2=3.0 Hz, 1H, H–6); 2.12 (s, 3H, OCH_3); 1.74 (d, J=13.0 Hz, 1H, H–8); 1.52 (m, 4H, H–19, H–20); 1.22, s (3H, CH_3); 1.05 (s, 3H, CH_3) ppm.

N–[4–[4–(2–methoxyphenyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximide dihydrochloride III·2HCl

Compound **III** was dissolved in anhydrous methanol saturated with gaseous HCl and left at ambient temperature for 1h. Diethyl ether was added dropwise to precipitate colorless solid, m.p. 212–216°C.

$C_{29}H_{41}Cl_2N_3O_6$ (596.65)

N–[4–[4–phenyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximide (IV): m.p. 128–130°C (hexane). Yield 58.0%.

$C_{28}H_{37}N_3O_5$ (525.65)

IR (KBr) cm^{-1} 1740, 1680 (C=O); ^1H NMR ($CDCl_3$) δ 7.30–7.20 (m, 2H, ArH); 6.96–6.80 (m,

3H, ArH); 4.16 (dd, J_1=10.2 Hz, J_2=2.0 Hz, 1H, H–2); 3.50 (t, J=6.6 Hz, 2H, H–18); 3.39 (dd, J_1=10.2 Hz, J_2=3.4 Hz, 1H, H–3); 3.19 (m, 4H, piperazine); 2.66–2.52 (m, 6H, piperazine–H. H–6, H–8); 2.51 (d, J=3.4 Hz, 1H, H–4); 2.38 (t, J=7.0 Hz, 2H, H–21); 2.24 (dd, J_1=19.5 Hz; J_2=2.9 Hz, 1H, H–6); 2.12 (s, 3H, H–15); 1.74 (d, J=13.2 Hz, 1H, H–8); 1.51 (m, 4H, H–19, H–20); 1.22, s (3H, CH_3); 1.05 (s, 3H, CH_3) ppm.

N–[4–[4–methyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octane–2,3–dicarboximide (V): m.p. 82–84°C (hexane). Yield 43.0%.

$C_{23}H_{35}N_3O_5$ (433.55)

IR (KBr) cm^{-1} 1760, 1680 (C=O); ^1H NMR ($CDCl_3$) 4.16 (dd, J_1=9.8 Hz, J_2=2.0 Hz, 1H, H–2); 3.48 (t, m, 2H, H–18); 3.40 (dd, J_1=9.8 Hz, J_2=3.9 Hz, 1H, H–3); 2.60–2.30 (m, 8H, piperazine); 2.59 (dd, J_1=19.5 Hz, J_2=1.95 Hz, 1H, H–6); 2.55 (dd, J_1=13.2 Hz; J_2=3.4 Hz, 1H, H–8); 2.53 (d, J=3.9 Hz, 1H, H–4); 2.33 (t, J=7.6 Hz, 2H, H–21); 2.28 (s, 3H, N–CH_3), 2.12 (s, 3H, H–15), 2.24 (dd, J_1=19.5 Hz; J_2=3.4 Hz, 1H, H–6); 1.74 (d, J=13.2 Hz, 1H, H–8); 1.52–1.43 (m, 4H, H–19, H–20); 1.22, s (3H, CH_3); 1.05 (s, 3H, CH_3) ppm.

N–[4–[4–(*p*–flurophenyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan5–one–2,3–dicarboximide (VI): m.p. 125–127°C (hexane). Yield 62%.

$C_{28}H_{36}N_3FO_5$ (513.61)

IR (KBr) cm^{-1} 1770, 1660 (C=O); ^1H NMR ($CDCl_3$) δ 7.00–6.85 (m, 4H, ArH); 4.16 (dd, J_1=9.8 Hz, J_2=2.4 Hz, 1H, H–2); 3.50 (t, J=6.8 Hz, 2H, H–18); 3.40 (dd, J_1=9.8 Hz, J_2=3.9 Hz, 1H, H–3); 3.11 (t, J=4.9 Hz, 4H, piperazine–H); 2.66–2.50 (m, 8H, piperazine–H, H–6, H–8); 2.53 (d, J=3.9 Hz, 1H, H–4); 2.38 (t, J=7.1 Hz, 2H, H–21); 2.24 (dd, J_1=19.3 Hz; J_2=3.2 Hz, 1H, H–6); 2.11 (s, 3H, H–15), 1.74 (d, J=13.0 Hz, 1H, H–8); 1.51 (m, 4H, H–19, H–20); 1.22, s (3H, CH_3); 1.06 (s, 3H, CH_3) ppm.

N–[4–[4–(benzyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximide (VII): m.p. 93–95°C (hexane). Yield 57%.

$C_{29}H_{39}N_3O_5$ (551.66)

IR (KBr) cm^{-1} 1720, 1660 (C=O); ^1H NMR ($CDCl_3$) δ 7.32–7.22 (m, 5H, ArH); 4.15 (dd, J_1=10.2 Hz, J_2=2.0 Hz, 1H, H–2); 3.47 (t, J=6.8 Hz, 2H, H–18); 3.50 (s, 2H, CH_2Ar); 3.38 (dd, J_1=10.2 Hz, J_2=3.4 Hz, 1H, H–3); 2.64–2.34 (m, 10H, piperazine–H, H–6, H–8); 2.52 (d, J=3.4 Hz, 1H, H–4); 2.32 (t, J=7.3 Hz, 2H, H–21); 2.22 (dd, J_1=19.5 Hz; J_2=2.9 Hz, 1H, H–6); 2.11 (s, 3H, H–15); 1.73 (d, J=13.2 Hz, 1H, H–8); 1.47 (m, 4H, H–19, H–20); 1.21, s (3H, CH_3); 1.04 (s, 3H, CH_3) ppm.

N–[4–[4–(pirydyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximide (VIII): m.p. 142–144°C (hexane). Yield 64%.

$C_{27}H_{36}N_4O_5$ (406.61)

IR (KBr) cm^{-1} 1740, 1680 (C=O); ^1H NMR ($CDCl_3$) δ 8.18 (m, 1H, $H_{\alpha pyridine}$); 7.47 (m, 1H, $H_{\gamma pyridine}$); 6.62 (m, 1H, $H_{\beta pyridine}$); 4.16 (dd, J_1=9.8 Hz, J_2=2.4 Hz, 1H, H–2); 3.54 (t, J=4.8 Hz, 2H, piperazine–H); 3.51 (t, J=8.0 Hz, 2H, H–18); 3.40 (dd, J_1=9.8 Hz, J_2=3.4 Hz, 1H, H–3); 2.60–2.48 (m, 6H, piperazine–H, H–4, H–8); 2.60 (dd, J_1=19.6 Hz; J_2=2.4 Hz, 1H, H–6); 2.37 (t, J=7.1 Hz, 2H, H–21); 2.24 (dd, J_1=19.6 Hz; J_2=3.0 Hz, 1H–6); 2.12 (s, 3H, H–15); 1.74 (d, J=13.2 Hz, 1H, H–8); 1.52 (m, 4H, H–19, H–20); 1.22, s (3H, CH_3); 1.05 (s, 3H, CH_3) ppm.

N–[4–[4–(pirymidyl)–1–piperazinyl]butyl]–1–acetoxy–7,7–dimethylbicyclo[2.2.2]octan–5–one–2,3–dicarboximide (IX): m.p. 144–147°C (hexane). Yield 75%.

$C_{29}H_{39}N_3O_6$ (497.60)

IR (KBr) cm^{-1} 1740, 1680 (C=O); ^1H NMR ($CDCl_3$) δ 8.30 (d, J=4.4 Hz, 2H, $H_{\alpha pyrimidine}$); 6.47 (dd, J=4.6 Hz, 1H, $H_{\beta pyrimidine}$); 4.17 (dd, J_1=10.2 Hz, J_2=2.0 Hz, 1H, H–2); 3.82 (t, J=5.1 Hz, 2H, piperazine–H); 3.54 (t, J=4.8 Hz, 2H, piperazine–H); 3.50 (t, J=6.8 Hz, 2H, H–18); 3.40 (dd, J_1=10.2 Hz, J_2=3.9 Hz, 1H, H–3); 2.60 (dd, J_1=19.5 Hz; J_2=2.0 Hz, 1H, H–6); 2.54 (d, J=3.4 Hz, 1H, H–4); 2.50 (dd, J_1=12.7 Hz; J_2=3.4 Hz, 1H, H–8); 2.48 (t, J=5.1 Hz, 2H, piperazine–H); 2.37 (t, J=7.1 Hz, 2H, H–21); 2.24 (dd, J_1=19.5 Hz; J_2=3.4 Hz, 1H, H–6); 2.12 (s, 3H, H–15); 1.74 (d, J=12.7 Hz, 1H, H–8); 1.52 (m, 4H, H–19, H–20); 1.22, s (3H, CH_3); 1.05 (s, 3H, CH_3) ppm.

The compound **III·2HCl** was tested for CNS activity by Krząścik, Piasecki and Kostowski in the Institute of Psychiatry and Neurology in Warsaw, Poland. Wistar male rats, bought from a licensed breeder, weighing 200–250 g were used in all experiments. They were housed in groups of 8 with unlimited access to tap water and food.

Writh's test

Compound **III·2HCl** was injected intraperitoneally at a dose of 10.0 mg/kg. Haloperidol (0.4 mg/kg) was used as reference drug 30, 60, 90, 150 and 240 min after dosing, forepaws of each rats were placed

Table 1. Duration of immobility [s], mean values obtained from 6–8 experiments ± SEM.

Compound	Time after dosing				
	30 min	60 min	90 min	150 min	240 min
Vehicle (H_2O)	4.3 ± 2.6	7.8 ± 2.7*	9.8 ± 3.6	14.7 ± 4.4	13.7 ± 4.7
Haloperidol (0.4 mg/kg)	9.8 ± 1.2	72.2 ± 34.2*	102.8 ± 34.1*	110.7 ± 32.2*	171.7 ± 8.3*
Compound **III·2HCl**	13.0 ± 3.8*	17.2 ± 6.3*	21.5 ± 10.2*	41.2 ± 21.4*	30.7 ± 15.6*

*$p<0.05$ *v.s.* H_2O.

Table 2. Effect of compound **III·2HCl** on open field activity.

	General locomotor activity (number of photobeam interrupted)	Open field activity (number of entries into the central part during 10 min)	Number of holes penetrated	Time of staying in the open field
Vehicle (H_2O	97 ± 11	6.8 ± 1.2	12.3 ± 3.4	10.8 ± 2.6
Compound **III·2HCl**	40 ± 11.9*	1.0 ± 0.6*	3.7 ± 0.9*	1.7 ± 1.7*

*$p<0.05$ *v.s.* H_2O

on an elevated bar. Duration of immobility during 3–min testing period (catalepsy) was recorded.

Vogel's conflict test

Adult male Wistar rats were water deprived daily for 23 h during 4 days preceding the test session. Compound **III·2HCl** was injected interperitoneally at a dose of 10.0 mg/kg, 30 min before testing. Then, thirsty animals while drinking, were given, during a 15 min session, a series of mild electric shocks (0.4 mA, 4 s long trains of impulses divided by 5 s a long intervals), when completing the shock circuit through the rat body. The amount of consumed water was taken as a measure of conflict behavior.

Porsolt's test

On the first day the rats were placed individually for 15 min into a glass cylinder (height 40 cm, diameter 16 cm) containing 20 cm of water, maintained at 24°C. The animals were treated 24, 5 and 1 h before water immersion. Compound **III·2HCl** was injected interaperitoneally at a dose level of 1.0 and 10.0 mg/kg. Dezipramine was used as reference drug. Duration of mobility during a 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.

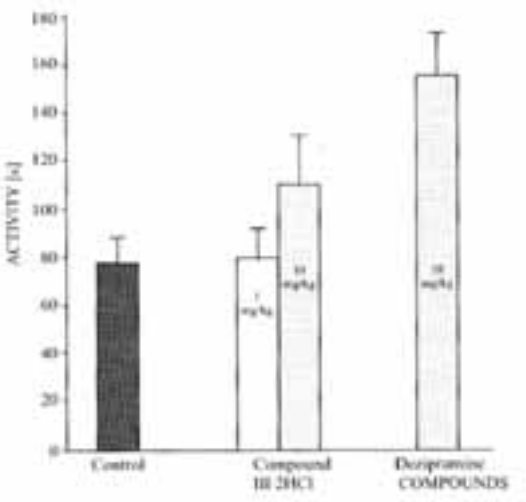


Figure 2. The effect of compound **III·2HCl** on rat behavior in the Porsolt test. The data are shown as mean ±SEM. ***$p < 0.001$ related to control group (water).

Open field locomotor activity

This activity was measured in Wistar rats weighing 220–240 g, after the appropriate treatment with compound **III·2HCl**. This compound was injected intraperitoneally at a dose level of 10.0 mg/kg 30 min before testing. Water was injected to the control group of rats. The apparatus consisted of a round arena box 80 cm diameter, 3 photosensors and recording system. The animals were maintained in an animal house for one week 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 interruption), number of entries into the central part of the open field and time of stay in the central part.

Statistic analysis

The data obtained from FBP and LLR, open field and Porsolt's test were analyzed by the Student t–test. The results obtained from Vogel's test were analyzed by Newman–Keuls' test.

RESULTS

The administration of compound **III·2HCl** (10 mg/kg) 60 min before behavioral evaluation did not alter FBP but induced weak LLR. It did not stimulate the serotoninergic system, especially 5–HT_{1A} receptor.

In Writh's test compound **III·2HCl** (10 mg/kg) showed a strong sedative effect, induced ptosis, increased muscle tonus and induced a weak cataleptogenic effect (Table 1).

Compound **III·2HCl** did not display real anxiolytic activity in the Vogel conflict test.

It increased motor activity in the stress situation in Porsolt's test, which may be interpreted as a weak antidepressive activity (Figure 2).

In the open field test, it decreased the general activity, number of entries into the central part, time of staying in the central part of the open field and number of holes penetrated (Table 2).

REFERENCES

1. Nelson D.L.: Pharmacol. Biochem. Behav. 40, 1041 (1991).
2. Glennon R.A.: Drug Dev. Res. 26, 251 (1992).
3. Kossakowski J., Zawadowski T., Balicka E.: Acta Polon. Pharm. – Drug Res. 54 (6), 479 (1997).
4. Kossakowski J., Zawadowski T., Kuśmierczyk J.: Acta Polon. Pharm. – Drug Res. 55 (4), 315 (1998).
5. Kossakowski J., Kuśmierczyk J.: Acta Polon. Pharm. – Drug Res. 56 (Suppl.), 94 (1999).
6. Kossakowski J., Kuśmierczyk J.: Pharmazie 1, 5 (2000).
7. Kossakowski J., Hejchman E.: Acta Polon. Pharm. – Drug Res. 57 (Suppl.), 57 (2000).
8. Kossakowski J., Krawiecka M.: Acta Polon. Pharm. – Drug Res. 57 (Suppl.), 53 (2000).
9. Kossakowski J., Jarocka M.: Farmaco 56, 785 (2001).
10. Berendsen H.G., Jenck R., Broekamp C.L.E.: Pharmacol. Biochem. Behav. 33, 821 (1989).
11. Berendsen H.G., Broekamp C.L.E.: Br. J. Pharmacol. 101, 667 (1990).
12. Writh W.R., Grosswald R., Horein V., Risse K.H.: Arch. Int. Pharmacodyn. 1, 115 (1978).
13. Shimizu H., Hirose A., Tatsuno T., Nakamura M., Katsube J.: Japan J. Pharmacol. 45, 493 (1987).
14. Porsolt R.D., Anton G., Blavet N., Jalfre M.: Eur. J. Pharmacol. 47, 379 (1978).
15. Jessa M., Nazar M., Płaźnik A.: Pol. J. Pharmacol. 47, 81 (1995).

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