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SYNTHESIS OF NEW N–[4–(4–ARYL– AND 4–HETEROARYL–1–PIPERAZINYL)BUTYL]DERIVATIVES OF 1–METHYL–5–OXOBICYCLO[2.2.1]HEPTANE–2,3–DICARBOXIMIDE WITH AN EXPECTED ANXIOLYTIC ACTIVITY

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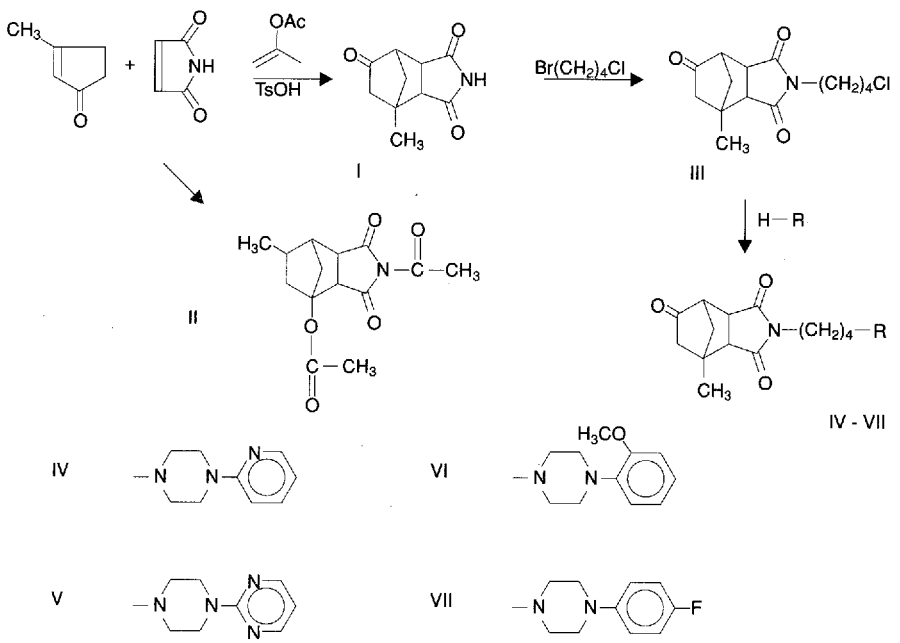
Abstract: Preparation of a number of derivatives of 1–methyl–5–oxobicyclo[2.2.1]heptane–2,3–dicarboximide with a potential anxiolytic activity has been described. New analogs of Tandospirone *i.e.* derivatives of bicyclo[2.2.1]heptane (10), were aimed at.

Keywords: Derivatives of 1–methyl–5–oxobicyclo[2.2.1]heptane, synthesis.

The new generation anxiolytics (buspirone, gepirone, ipsapirone, tandospirone, and other) display high affinity for the 5–HT_{1A} and D_2 receptor types (1, 2) and therefore are widely used in the treatment of psychotic and neurotic disorders. Many analogs have been synthesized (3–5) and those containing the 4–aryl/heteroaryl–piperazinylalkyl group attached to a cyclic imide have demonstrated an anxiolytic activity (1, 2). Our compounds are structuraly similar to Tandospirone (10). In the research intendend for developing more selective therapeutic agents the dopaminergic system is assumed to be more sensitively modulated through pharmacological manipulation of the serotoninergic system (6–9).

Continuing our chemical and pharmacological studies on the syntheses of imides endowed with anxiolytic activity, we prepared a number of N–4[–(4–aryl– and 4–heteroaryl–1–piperazinyl)butyl]derivatives of 1–methyl–5–oxobicyclo [2.2.1] heptane–2,3–dicarboximide. The starting compounds were 3–methylcyclopentanone and maleimide which were condensed to yield 1–methyl–5–oxobiocyclo[2.2.1]heptane–2,3–dicarboximide [I]. In the reaction with 1–bromo–4–chlorobutante in methylethylketone and in the presence of



anhydrous potassium carbonate, a 4–chrorobutyl derivative [**III**] was further condensed with various 4–aryl– and 4–heteroaryl piperazines in acetonitrile in the presence of anhydrous potassium carbonate to yield compounds [**IV–VII**] (Scheme 1).

The compounds obtained were tested for CNS activity at the Departament of Pharmacology of the Military Institute of Hygiene and Epidemiology. (headed by Prof. S. Rump).

Their affinity for the rat brain receptor 5–HT_{1A} was determined in vitro with [^{3}H]8–OH–DPAT and buspirone as the radioligand and the reference, respectively. The compound with highest affinity [**V**] was characterized by Ki=$1.93 \cdot 10^{-5}$M. Results of pharmacological studies will be published elsewhere.

EXPERIMENTAL

Melting points were determined in a Kofler's capillary apparatus.

IR spectra were recorded on a Specord 75 IR spectrophotometer in KBr pellets; ^{1}H NMR spectra: UNITY plus 200 VARIAN's, 200 MHz apparatus, were registered in $CDCl_3$. Thin–layer chromatography was performed on Merck Kieselgel 60, F–254 plates.

Synthesis of 1–methyl–5–oxobicyclo[2.2.1]heptane–2,3–dicarboximide [**I**] and N–acetyl–1–acetoxy–5–methyl–bicyclo[2.2.1]hept–5–ene–2,3–dicarboximide [**II**]

A mixture of 0.02 mol (1.96 g) 3–methylcyclopentanone, 0.02 mol (1.94 g) maleimide (20% excess), and 50 mg p–toluenesulfonic acid was heated for 22 h with 10 cm^3 of isopropenyl acetate. The solvent was removed in a rotary evaporator. The residue was crystallized from ethylene acetate. Compound [**I**] formed a precipitate and was filtred off, and some time later compound [**II**] crystallized from the filtrate and was separated.

^{1}H NMR of [**I**] see Table 2, ^{1}H NMR ($CDCl_3$) of [**II**]: 2.17 (s.3H), 3.49 (dd, 1H, J~8.7 and 5.0), 3.86 (d, 1H, J~8.7), 3.17 (m.1H), 1.80 (d,3H, J~1.9), 5.81 (m.1H), 2.24 (d, 2H, J~1.9), 2.45 (s. 3H,–N –CO–CH_3).

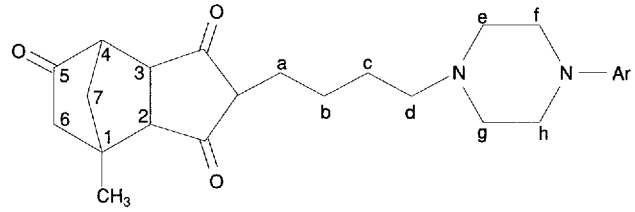
Synthesis of N–(4–chlorobutyl)–1–methyl–5–oxobicyclo[2.2.1]heptane–2,3–dicarboximide [**III**]

A mixture of 0.01 mol (2.4 g) 1–methyl–5–oxobicyclo[2.2.1]heptane–2,3–dicarboximide [**I**], 0.01 mole (2.2 g) 1–bromo–4–chlorobutane, 2.4 g of K_2CO_3 40 cm^3 of methyl ethyl ketone was refluxed for 50 h. The hot mixture was filtered and the solvent was removed in

Table 1. Physical, analytical and IR spectral data of compounds [**I–VII**]

Comp. No.	Formula Mol. weight	Solvent m.p., °C	Yield %	Analysis Calcd./Found %C	%H	%N	IR(KBr) cm^{-1}
I	$C_{10}H_{11}NO_3$ 193.20	ethyl acetate 199–201	18	62.17 61.99	5.75 5.61	7.25 7.29	C=O 1695
II	$C_{14}H_{15}NO_5$ 277.28	ethyl acetate 147–148	2	60.65 60.32	5.42 5.61	5.05 5.06	C=O 1695; 1640
III	$C_{14}H_{18}NO_3Cl$ 283.79	hexane 56–59	72	59.24 59.14	6.39 6.32	4.94 5.00	C=O 1670
IV	$C_{23}H_{30}N_4O_3$ 410.50	heptane 145–146	69	67.29 67.29	7.37 7.31	13.65 13.72	C=O 1685
V	$C_{22}H_{29}N_5O_3$ 411.49	heptane 135–136	55	64.21 64.19	7.10 7.03	17.02 17.30	C=O 1670
VI	$C_{25}H_{33}N_3O_4$ 439.54	heptane 97–99	71	68.30 68.30	7.57 7.55	9.56 9.81	C=O 1680
VII	$C_{24}H_{30}N_3O_3F$ 427.51	heptane 121–122	60	67.42 67.45	7.07 7.10	9.83 9.82	C=O 1675

Table 2. ^{1}H NMR spectroscopic data of compounds [I and III–VII]



Imide and N–butylimide moiety

Compd. Solv.	1 –CH_3	2	3	4	6	7	a	b/c	d	–NH
I $CDCl_3$	1.54 3H (s)	3.09 1H (m.)	3.51 1H (dd.) J~10.0 and 6.2	3.09 1H (m.)	2.16 2H (m.)	1.93 2H (m.)	–	–	–	8.35 1H (m.)
III $CDCl_3$	1.55 3H (s)	2.95–3.15 1H (m.)	3.32–3.62 1H (m.)	2.95–3.15 1H (m.)	1.90–2.07 2H (m.)	1.90–2.07 2H (m.)	3.32–3.62 2H (m.)	1.71 2H (m.)	3.32–3.62 2H (m.)	–
IV $CDCl_3$	1.54 3H (s)	2.95–3.15 1H (m.)	3.35–3.62 1H (m.)	2.95–3.15 1H (m.)	1.90–2.10 2H (m.)	1.90–2.10 2H (m.)	3.35–3.62 2H (m.)	1.52 2H (m.)	2.30–2.62 2H (m.)	–
V $CDCl_3$	1.54 3H (s)	2.91–3.14 1H (m.)	3.34–3.54 1H (m.)	2.91–3.14 1H (m.)	1.89–2.07 2H (m.)	1.89–2.07 2H (m.)	3.34–3.54 2H (m.)	1.52 2H (m.)	2.22–2.56 2H (m.)	
VI $CDCl_3$	1.55 3H (s)	3.07 1H (d) J=6.0	3.42–3.47 1H (m.)	3.00 1H (dd.) J=9.0 and 2.0	1.88–2.08 2H (m.)	1.88–2.08 2H (m.)	3.42–3.47 2H (m.)	1.51 2H (m.)	2.40 2H (t.) J~7.0	–
VII $CDCl_3$	1.56 3H (s)	3.07 1H (d) J=6.0	3.42–3.47 1H (m.)	3.00 1H (dd.) J=9.0 and 1.5	1.88–2.08 2H (m.)	1.88–2.08 2H (m.)	3.42–3.47 2H (m.)	1.51 2H (m.)	2.39 2H (t.) J~7.0	–

Table 2. Cont. N-arylpiperazine moiety

Compd. Solv.	e/g	f/h	Ar				
IV $CDCl_3$	2.30-2.62 2H (m)	3.35-3.62 2H (m)	–	8.17 1H (m.) HAr;	6.62 1H (m.) HAr	7.47 1H (m.) HAr	6.62 1H (m.) HAr
V $CDCl_3$	2.22-2.56 2H (m.)	3.81 2H (t) J~5.0	–	8.27 1H (d) J~4.7 HAr	6.46 1H (t) J~4.7 HAr	8.27 1H (d) J~4.7 HAr	–
VI $CDCl_3$	2.64 2H (m)	~3.09 2H (m)	3.86[3H](s)-OH_3; 6.84-7.01[4H](m.)HAr				
VII $CDCl_3$	2.59 2H (t) J~5.0	3.11 2H (t) J~5.0	6.95 1H (m.) HAr	6.87 1H (m.) HAr	–	6.87 1H (m.) HAr	6.95 1H (m.) HAr

a rotary evaporator. The residue was crystallized from hexane.

General method of preparing N–[4–(4–aryl– and 4–heteroaryl–1–piperazinyl)butyl] derivatives [**IV–VII**]

A mixture of 0.00035 mol (1g) of N–(4–chlorobutyl)–1–methyl–5–oxobicyclo[2.2.1]heptane–2,3–dicarboximide (**III**), 0.00035 mol of an appropriate amine, 1 g anhydrous K_2CO_3, and 0.25 g KI was refluxed in 30 cm^3 of acetonitrile for 30 h. The inorganic precipitate was filtered off and the solvent was removed in a rotary evaporator. The residue was crystallized from heptane to yield compounds [**IV–VII**].

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