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Synthesis of new derivatives of 1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide with an expected anxiolytic activity

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The preparation of a number of derivatives of 1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide with potential anxiolytic activity has been described. The aim of our study was to obtain new analogues of tandospirone, that is derivatives of cyclic imides [1].

1. Introduction

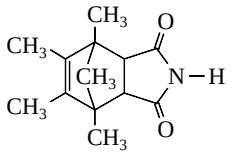
The best anxiolytic drug without side effects is still being investigated. A new generation of anxiolytics are derivatives of buspirone. Buspirone and derivatives (gepirone, ipsapirone, tandospirone and others) demonstrate an efficiency comparable to diazepam [1], but without benzodiazepine-related side effects such as sedation, muscle relaxation, alcohol potenciation and abuse liability [2].
Buspirone displays high affinity for the 5-HT_{1A} and D_2 receptor types [1, 3] and are therefore widely used in the treatment of psychotic and neurotic disorders. The new analogue we synthesised, containing the 4-aryl-/4-heteroaryl-piperazinylalkyl group attached to a cyclic imide, demonstrated an anxiolytic activity [1, 3].
As a result of our studies, we decided to synthesize a number of new derivatives of 1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide.

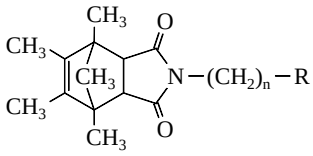
2. Investigations, results and discussion

2.1. Chemistry

The desired compound **3** was synthesised in a Diels-Alder reaction. The starting compound was 1,2,3,4,5-pentamethylcyclopentadiene (**1**), which was heated with maleimide (**2**). *N*-(4-chlorobutyl)-, *N*-(3-bromopropyl)- and *N*-(2-bromoethyl)-1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximides **4**–**6** have been formed by the alkylation of imide **3** with 1-bromo-4-chlorobutane, 1,3-dibromopropane and ethylene bromide. The bromine derivatives were further condensed with N-methylamines and 4-aryl- and 4-heteroaryl piperazines in appropriate solvents, in the presence of potassium carbonate to yield compounds **7**–**19** (Scheme).
Compounds **3**–**19** are described in the Table. The new compounds were identified and proven by ^{1}H NMR and IR spectra and elemental analyses.

Table: Physical constants and analytical data of compounds 3–19





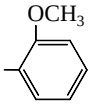
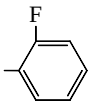
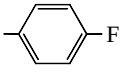
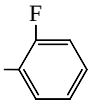
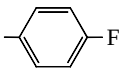
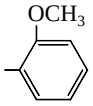
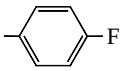
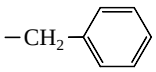
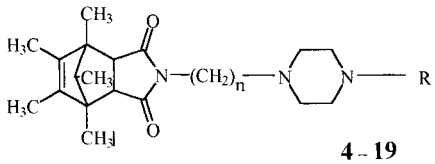
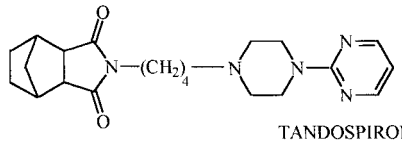
Compd.	R	n	Formula Mol.wt.	M.p. (°C) Solvent	Yield (%)
3	–	–	$C_{14}H_{19}NO_2$ 233.3	180–181 heptane	90
4	Cl	4	$C_{18}H_{26}ClNO_2$ 323.9	41–43 heptane	52
5	Br	3	$C_{17}H_{24}BrNO_2$ 354.3	135 °C/0.05 mmHg vacuum distillation	49
6	Br	2	$C_{17}H_{22}BrNO_2$ 340.2	57–60 hexane	61
7		2	$C_{27}H_{39}Cl_2N_3O_3$ 542.5	214–217 methanol/ether	80
8		2	$C_{26}H_{35}FClN_3O_2 \cdot 0.25\ H_2O$ 485.1	226–229 Methanol/ether	82
9		2	$C_{26}H_{34}FN_3O_2 \cdot 1\ H_2O$ 457.6	64–66 hexane	85
10		3	$C_{27}H_{37}FClN_3O_2$ 499.0	160–162 methanol/ether	81

Table: Physical constants and analytical data of compounds 3–19 (cont.)

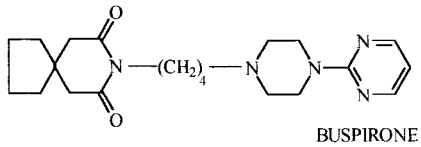
Compd.	R	n	Formula Mol.wt.	M.p. (°C) Solvent	Yield (%)
11		3	$C_{27}H_{38}FCl_2N_3O_2 \cdot 2\,H_2O$ 562.5	201–203 methanol/ether	79
12	$-CH_3$	3	$C_{22}H_{37}Cl_2N_3O_2$ 464.5	235–236 methanol/ether	82
13		4	$C_{28}H_{39}N_3O_2$ 449.6	86–87 hexane	76
14		4	$C_{28}H_{42}ClN_3O_3$ 516.2	181–183 hexane	74
15		4	$C_{28}H_{38}FN_3O_2$ 467.6	102–103 hexane	69
16		4	$C_{26}H_{37}N_5O_2$ 451.6	90–91 hexane	74
17		4	$C_{29}H_{43}Cl_2N_3O_2 \cdot 1\,H_2O$ 554.6	234–237 methanol/ether	78
18		4	$C_{27}H_{40}Cl_2N_4O_2$ 532.6	120–123 methanol/ether	80
19	$-CH_3$	4	$C_{23}H_{39}Cl_2N_3O_2$ 460.67	265–267 methanol/ether	82



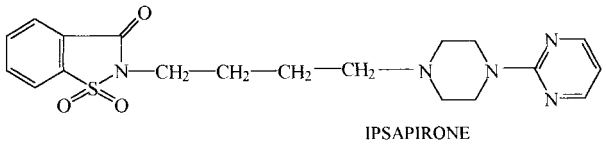
4 - 19



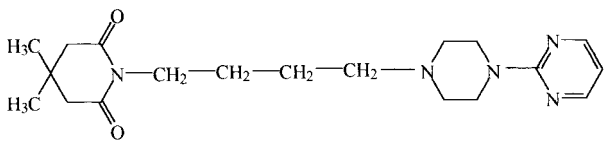
TANDOSPIRONE



BUSPIRONE



IPSAPIRONE



GEPIRONE

2.2. Pharmacology

Compound **14** was transformed into the hydrochloride, and submitted to a primary screening test of its 5-HT_{1A} receptor affinity, general (Open Field Test [4]), neuroleptic (Writh's test [5]) and antidepressive (Porsolt test [6]) activity. This compound did not display real anxiolytic activity in the "Open Field Test" and the test described by Vogel. It displayed a low neuroleptic activity. An antidepressive activity was not observed.

The compounds obtained were tested for CNS activity in the Institute of Psychiatry and Neurology. Wistar rats of either sexes weighing 200–250 g were used in all experiments. They were housed in groups of 8. The compounds were injected intraperitoneally at the dose level from 1 mg/kg to 10 mg/kg, in a constant 2 ml volume, before testing. Buspirone, haloperidol and dezipramine were used as reference drugs.

3. Experimental

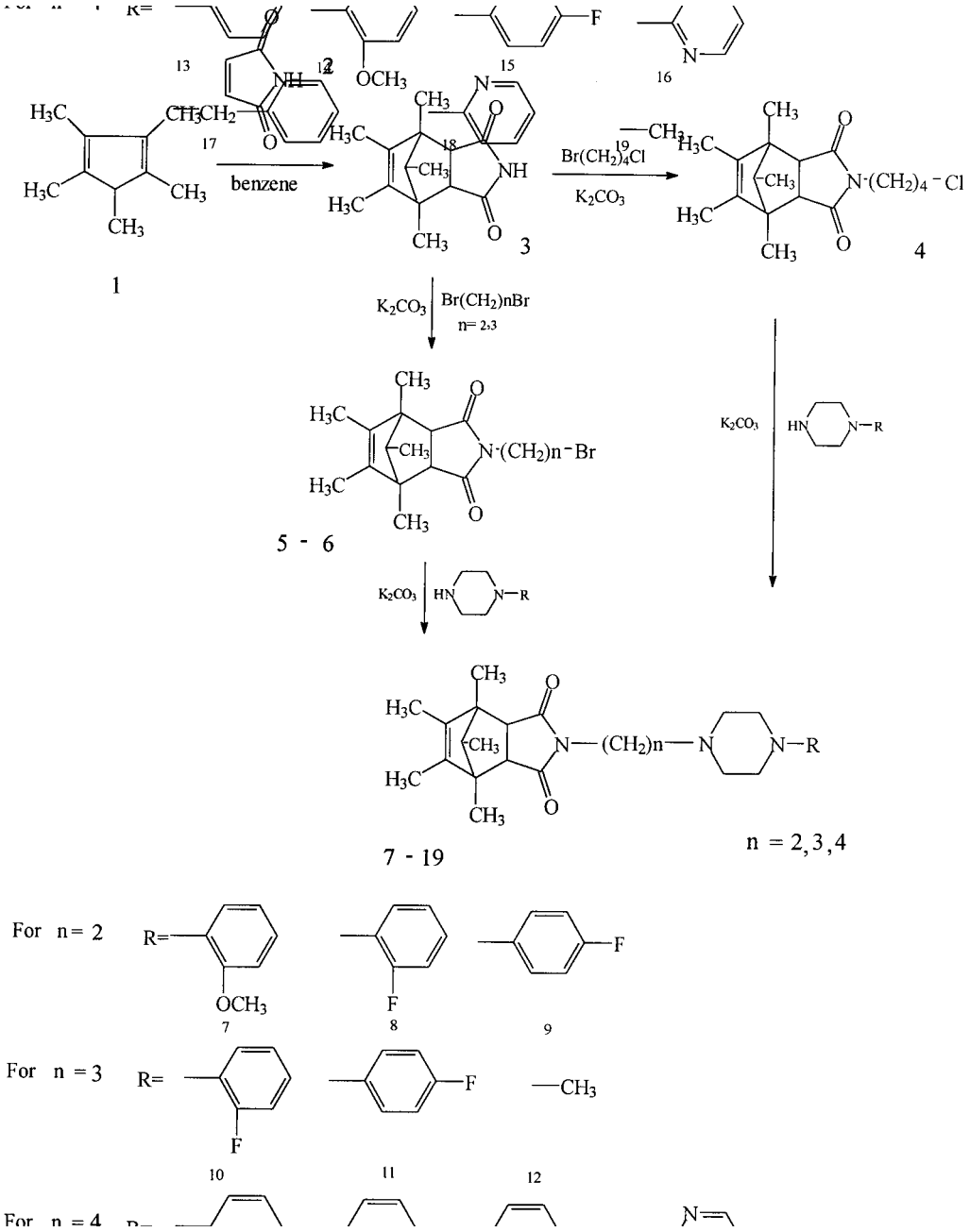
Melting points were determined in a capillary Kofler's apparatus. IR spectra were recorded on a Specord 75 IR spectrophotometer in KBr pellets; ^{1}H NMR spectra: UNITY plus 200 VARIAN's 200 MHz apparatus registered in $CDCl_3$ and DMSO. The results of elemental analyses (C, H, N) were within $\pm 0.4\%$ of the theoretical values. The IR spectrum of the compounds showed an absorption band at 1660 cm^{-1}–1760 cm^{-1} indicating the presence of C=O in the ring.

3.1. 1,2,3,4,7-Pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide (3)

1,2,3,4,5-Pentamethylcyclopentadiene (0.037 mol, 5.0 g) and maleimide (0.037 mol, 3.95 g) were heated for 20 min with 20 ml of benzene. The solvent was removed on a rotary evaporator. The residue was crystallised from heptane to give 7.27 g of compound **3**.

^{1}H NMR: 0.60 (d, [3 H], J = 6.8); 1.31 (s, [6 H]); 1.51 (q, [1 H]); 1.53 (s, [6 H]); 2.92 (s, [2 H]); 8.64, [1 H]; broad –NH.

Scheme



3.2. N-(4-Chlorobutyl)-1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide (**4**)

A mixture of 0.02 mol (4.8 g) of imide **3**, 0.02 mol (3.6 g) of 1-bromo-4-chlorobutane in 70 ml of ethyl methyl ketone was heated in the presence of 4.8 g of K_2CO_3 for 50 h. The hot mixture was filtered and the solvent was removed on a rotary evaporator. The residue was crystallised from heptane.
^{1}H NMR: 0.60 (d, [3 H], J = 6.3); 1.33 (s, [6 H]); 1.49 (q, [1 H]); 1.62 (m, [4 H]); 1.49 (s, [6 H]); 3.52 (t, [2 H], J = 6.3); 2.87 (s, [2 H]); 3.25 (t, [2 H], J = 7.0).

3.3. N-(3-Bromopropyl)-1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide (**5**)

A mixture of 0.015 mol (3.5 g) of imide **3**, 0.03 mol (3.0 ml) of 1,3-dibromopropane and 3.5 g of K_2CO_3 in 40 ml of ethyl methyl ketone were heated for 40 h. The hot mixture was filtered and the solvent was removed on a rotary evaporator. The oily residue was distilled.
^{1}H NMR: 0.60 (d, [3 H], J = 6.5); 1.33 (s, [6 H]); 1.49 (s, [6 H]); 1.57 (q, [1 H], J = 6.5); 2.90 (s, [2 H]); 3.43 (t, [2 H], J = 7.0); 1.94 (m, [2 H]); 3.30 (t, [2 H], J = 7.3).

3.4. N-(2-Bromoethyl)-1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximide (**6**)

A mixture of 0.03 mol (7.0 g) of compound **3**, 0.06 mol (11.27 g) of ethylene bromide in 80 ml of CH_3CN was heated in the presence of 7.0 g K_2CO_3 for 50 h. The hot mixture was filtered and the solvent was removed on a rotary evaporator. The residue was crystallised from hexane.
^{1}H NMR: 3.714 (t, [2 H], J = 7.4); 3.25 (t, [2 H]); 2.906 (s, [2 H]); 1.558 (q, [1 H], J = 6.4); 1.498 (s, [6 H]); 1.336 (s, [6 H]); 0.602 (d, [3 H]).

3.5. General method of preparing N-[2-(amine-/4-aryl-1-piperazinyl)-ethyl]-1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximides **7–9**

A mixture of 0.0018 mol (0.6 g) of compound **6**, 0.0018 mol of the amine, 0.6 g of anh. K_2CO_3 and 0.2 g of KI in 25 ml of CH_3CN were refluxed for 50 h. The inorganic precipitate was filtered off, and the solvent was removed on a rotary evaporator. The residue was crystallised from an appropriate solvent to yield compounds **7**–**9**.

^{1}H NMR of **7**: 7.84–7.96, 7.30–7.44, 6.94–7.10 (m, [4 H]); 4.004 (s, [3 H]); 3.722 (t, [2 H], J = 5.2); 3.358 (t, [2 H]); 3.50–4.16 (m, [8 H]); 3.262 (s, [2 H]); 1.612 (q, [1 H], J = 6.4); 1.458 (s, [6 H]); 1.314 (s, [6 H]); 0.584 (d, [3 H]).

^{1}H NMR of **8**: 12.594 (bs, [1 H]); 6.90–7.13 (m, [4 H]); 3.746 (t, [2 H], J = 5.8); 3.239 (s, [2 H]); 3.180 (t, [2 H]); 2.80–4.00 (m, [8 H]); 1.611 (q, [1 H], J = 6.6); 1.457 (s, [6 H]); 1.314 (s, [6 H]); 0.58 (d, [3 H]).

^{1}H NMR of **9**: 6.78–7.03 (m, [4 H]); 3.478 (t, [2 H], J = 7.2); 3.083 (t, [4 H], J = 5.0); 2.877 (s, [2 H]); 2.627 (t, [4 H]); 2.402 (t, [2 H]); 1.54 (q, [1 H], J = 6.4); 1.492 (s, [6 H]); 1.331 (s, [6 H]); 0.595 (d, [3 H]).

3.6. General method of preparing N-[3-(amine-/4-aryl-1-piperazinyl)-propyl]-1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximides **10–12**

A mixture of 0.0028 mol (1.0 g) of compound **5**, 0.0028 mol of the appropriate amine, 1.0 g of anh. K_2CO_3 and 0.2 g of KI were heated in 50 ml of ethyl methyl ketone for 30 h. The inorganic precipitate was filtered off, and the solvent was removed on a rotary evaporator. The residue was crystallised from an appropriate solvent to yield compounds **10**–**12**.

^{1}H NMR of **10**: 10.79 (bs, [1 H]); 6.80–7.40 (m, [4 H]); 3.251 (t, [2 H], J = 7.4); 2.975 (s, [2 H]); 3.0–3.62 (m, [10 H]); 1.758 (m, [2 H]); 1.59 (q, [1 H], J = 6.2); 1.443 (s, [6 H]); 1.249 (s, [6 H]); 0.534 (d, [3 H]).

^{1}H NMR of **11**: 11.528 (bs, [1 H]); 9.60 (bs, [1 H]); 6.95–7.18 (m, [4 H]); 2.976 (s, [2 H]); 2.95–3.80 (m, [12 H]); 1.798 (m, [2 H]); 1.586 (q, [1 H], J = 6.4); 1.447 (s, [6 H]); 1.248 (s, [6 H]); 0.533 (d, [3 H]).

^{1}H NMR of **12**: 3.14–3.76 (m, [10 H]); 3.245 (t, [2 H], J = 7.2); 2.965 (s, [2 H]); 2.797 (s, [3 H]); 1.62–1.80 (m, [2 H]); 1.583 (q, [1 H], J = 6.6); 1.445 (s, [6 H]); 1.242 (s, [6 H]); 0.53 (d, [3 H]).

3.7. General method of preparing N-[4-(amine-/4-aryl-/4-heteroaryl-1-piperazinyl)butyl]-1,2,3,4,7-pentamethylbicyclo[2.2.1]hept-2-ene-5,6-dicarboximides **13–19**

Compound **4** (0.003 mol, 1.0 g), 0.003 mol (0.6 g) of the appropriate amine, 1.0 g of anh. K_2CO_3 and 0.2 g of KI in 50 ml of CH_3CN were refluxed for 30 h. The hot mixture was filtered, and the solvent was removed on a rotary evaporator. The residue was crystallised from an appropriate solvent to yield compounds **13**–**19**.

^{1}H NMR of **13**: 0.59 (d, [3 H], J = 6.6); 1.33 (s, [6 H]); 1.37–1.62 (m, [1 H]); 1.37–1.62 (m, [4 H]); 1.48 (s, [6 H]); 2.37 (t, [2 H], J = 7.5); 2.57 (m, [4 H]; 2.85 (s, [2 H]); 3.31 (t, [2 H], J = 7.5); 3.19 (m, [4 H]); 6.77 to 7.00 (m, [3 H]); 7.24–7.37 (m, [2 H]).

^{1}H NMR of **14**: 0.60 (d, [3 H], J = 6.3); 1.33 (s, [6 H]); 1.37–1.67 (m, [1 H]); 1.37–1.67 (m, [2 H]) + 1.94 (m, [2 H]); 1.47 (s, [6 H]); 3.04 (m, [2 H]); 3.04 (m, [2 H]) + 3.51 (m, [2 H]); 2.90 (s, [2 H]); 3.32 (t, [2 H], J = 7.3); 3.51 (m, [4 H]); 3.87 (s, [3 H]) $-OCH_3$; 6.77–7.05 (m, [4 H]).

^{1}H NMR of **15**: 0.59 (d, [3 H], J = 6.3); 1.33 (s, [6 H]); 1.37–1.62 (m, [1 H]); 1.37–1.62 (m, [4 H]); 1.48 (s, [6 H]); 2.37 (t, [2 H], J = 7.5); 2.57 (m, [4 H]; 2.85 (s, [2 H]); 3.31 (t, [2 H], J = 7.5); 3.10 (m, [4 H]); 6.72 to 7.05 (m, [4 H]).

^{1}H NMR of **16**: 0.59 (d, [3 H], J = 6.3); 1.33 (s, [6 H]); 1.37–1.62 (m, [1 H]); 1.37–1.62 (m, [4 H]); 1.48 (s, [6 H]); 2.37 (t, [2 H], J = 7.5); 2.47 (t, [4 H], J = 5.0); 2.85 (s, [2 H]); 3.31 (t, [2 H], J = 7.5); 3.81 (t, [4 H], J = 5.0); 6.47 (t, [1 H], J = 4.8); 8.30 (d, [2 H], J = 4.7).

^{1}H NMR of **17**: 0.52 (d, [3 H], J = 6.4); 1.23 (s, [6 H]); 1.40 (s, [6 H]); 1.56 (q, [1 H], J = 6.4); 2.94 (s, [2 H]); 3.16 (t, [2 H], J = 7.1); 1.32 (m, [4 H]); 3.03 (m, [2 H]); 3.28–3.56 (m, [10 H]); 7.31 (m, [5 H]).

^{1}H NMR of **18**: 0.59 (d, [3 H], J = 6.4); 1.31 (s, [6 H]); 1.45 (s, [6 H]); 1.56 (q, [1 H], J = 6.4); 2.92 (s, [2 H]); 3.30 (t, [2 H], J = 7.3); 1.49 (m, [2 H]); 1.89 (m, [2 H]); 3.19 (m, [2 H]); 3.30 (m, [2 H]); 3.74 (m, [2 H]); 4.20 (m, [2 H]); 4.70 (m, [2 H]); 7.07 (t, [1 H], J = 6.6); 7.27 (d, [1 H], J = 9.4); 8.04 (t, [1 H], J = 7.8); 8.18 (d, [1 H], J = 6.4).

^{1}H NMR of **19**: 0.59 (d, [3 H], J = 6.3); 1.32 (s, [6 H]); 1.37–1.67 (m, [1 H]); 1.37–1.67 (m, [2 H]) + 1.82 (m, [2 H]); 1.46 (s, [6 H]); 3.13 (m, [2 H]); 3.75 (m, [4 H]); 2.91 (s, [2 H]); 3.30 (t, [2 H], J = 7.0); 3.75 (m, [4 H]); 2.94 (s, [3 H])$-N-CH_3$.

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