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Synthesis of new *N*-substituted cyclic imides with an expected anxiolytic activity. XVII. Derivatives of 1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide

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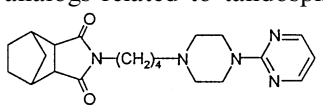
Abstract

The preparation of a number of derivatives of 1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide with potential anxiolytic activity has been described. The aim of our study was to obtain new analogs of tandospirone.

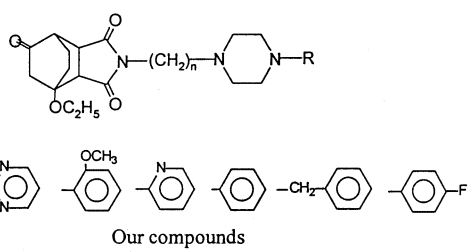
Keywords: Derivatives of 1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide; Anxiolytics

1. Introduction

The anxiolytics of generation II (buspirone, gepirone, ipsapirone, tandospirone and others) are 1-arylpiperazine derivatives with a high affinity to the 5-HT_{1A} receptor [1–3]. Therefore, they are widely used in the treatment of psychotic and neurotic disorders. Continuing our research in the field of 4-aryl/heteroaryl piperazinylalkyl derivatives [4–7], we have designed a number of new derivatives of 1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide. This paper describes the synthesis and the biological activities of a series of imide-modified analogs related to tandospirone [3].



Tandospirone



Our compounds

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2. Chemistry

The first step of the multistage synthesis was the reaction of 3-ethoxy-2-cyclohexen-1-one with maleimide, *p*-toluenosulfonic acid and isopropenyl acetate. A similar transformation was reported by Cimarusti and Wolinsky [8]. They used 1,3-diacetoxy-1,3-dienes generated in situ from cyclic 1,3-diketones, isopropenyl acetate and maleic anhydride to obtain 1-acetoxybicyclo[2.2.*X*]alkanedicarboxylic anhydride derivatives. 3-Ethoxy-2-cyclohexen-1-one in the presence of isopropenyl acetate was converted to 1-ethoxy-3-acetoxy-1,3-cyclohexadiene, which then served as the diene participant in a Diels–Alder reaction with maleimide. The mixture of adducts **1** and **1A** resulting from this reaction was hydrolyzed by heating with an 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** (Scheme 2). Compounds **1**–**15** are described in Table 2. The new compounds were characterized by ^{1}H NMR and IR spectra and elemental analysis.

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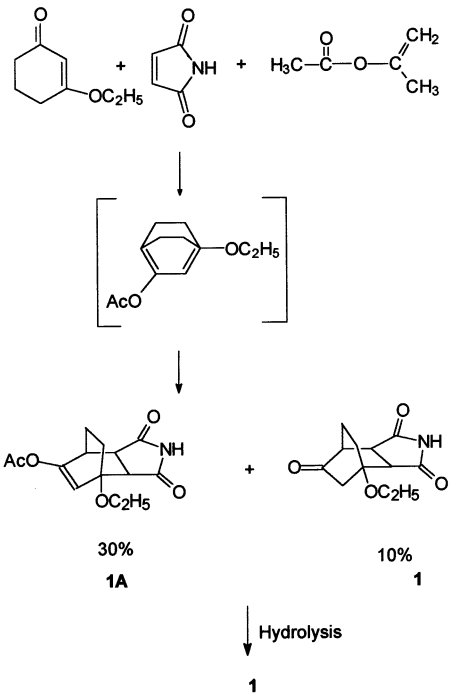
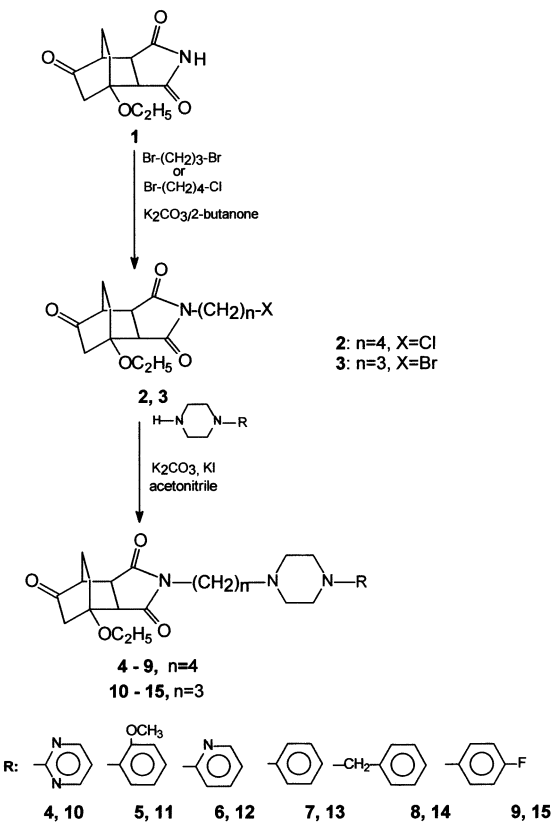


Scheme 1. Synthesis of 1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide.



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

Table 1
The effect of compounds **4** and **5** on rat behavior in the open fields test

Comp. dose (mg/kg)	Activity	Central entries	Time in central sector
4			
1	35.33 ± 6.69	1.17 ± 0.54	2.01 ± 1.37
5	36.33 ± 5.15	1.33 ± 0.61	4.02 ± 2.65
5		$^{*}P<0.05$	
1	41.51 ± 3.11	4.33 ± 1.15	4.58 ± 1.85
5	42.33 ± 5.98	1.17 ± 0.41	0.00 ± 0.00

The data are shown as mean $\pm$ SEM. The number of rats in the groups varied from eight to ten. $^{*} = P<0.05$ related to the control group.

3. Pharmacology

We selected two compounds containing 1-(2-pyrimidinyl)-piperazinylbutyl and 1-(*o*-methoxyphenyl)-piperazinylbutyl spacers for the pharmacological tests. Both groups are active on 5-HT_{1A} receptors [9,10]. The (*o*-methoxyphenyl)-piperazinylbutyl substituent is supposed to determine the structure of the active complex of the ligand with 5-HT_{1A} receptor, responsible for the antagonistic activity [11].

Compounds **4** and **5** were transformed into their hydrochlorides, and submitted to general (open field test) and antidepressive (Porsolt test) activity tests [12].

Open field locomotor activity [13] was measured in Wistar rats weighing 220–240 g, after the appropriate treatment with compounds **4** and **5**. These compounds were injected intraperitoneally at the dose level 1 and 5 mg/kg, in a 0.1 ml/100 g body weight volume before testing. NaCl (0.9%) was injected to the control group of rats. The apparatus consisted of a round arena box of 80 cm diameter, three photosensors and a recording system. The animals were maintained in the animal house for 1 week before the experiment. The behavior of animals was assessed for 10 min and recorded on 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 in glass cylinders (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 **4** and **5** were injected intraperitoneally at the dose level 1 and 5 mg/kg, in a 0.1 ml/100 g body weight volume before testing. NaCl (0.9%) was injected to the control group of rats. The duration of mobility during the 5-min testing period was recorded. A rat was con-

sidered to be mobile when it tried to make apparent attempts to escape from the cylinder.

3.1. Statistic analysis

The obtained data were analyzed by ANOVA followed by Student–Newman–Keuls test.

3.2. Results and discussion

Compound **4** did not present any anxiolytic action, but high anxiolytic and antidepressive activity was observed for compound **5**. Compound **5** (which was injected in a dose level of 1 mg/kg) increased ($P < 0.05$) a number of centers on the central sector of field, which tells us about anxiolytic activity (Table 1).

Compound **5** strongly stimulated the motor activity ($P < 0.001$) in Porsolt's test (Fig. 1). This property is consistent with antidepressant activity.

Compound **5** will be subjected to further tests to establish its full pharmacological profile.

4. Experimental

4.1. Chemistry

Melting points were determined in a capillary Kofler's apparatus and are uncorrected. IR spectra were recorded in a Specord 75 IR spectrophotometer (Zeiss, Jena) in KBr pellets; ^{1}H NMR spectra were recorded in

Table 2
Physicochemical properties of compounds **1–15**

Comp. no.	Yield (%)	Crystallization solvent	M.p. (°C)	Analyses
1	38	ethyl acetate	256–258	$C_{12}H_{15}NO_4$
2	72	hexane	89–91	$C_{16}H_{22}ClNO_4$
3	88	hexane	92–93	$C_{15}H_{20}BrNO_4$
4	75	methanol/ether	241–243	$C_{24}H_{35}Cl_2N_5O_4 \cdot 0.5H_2O$
5	80	methanol/ether	167–189	$C_{27}H_{39}Cl_2N_3O_5 \cdot 1H_2O$
6	56	hexane	114–116	$C_{25}H_{342}N_4O_4$
7	69	hexane	98–100	$C_{26}H_{35}N_3O_4$
8	81	hexane	103–105	$C_{22}H_{37}N_3O_4$
9	85	hexane	108–110	$C_{26}H_{34}FN_3O_4$
10	75	hexane	173–174	$C_{23}H_{33}Cl_2N_5O_4$
11	83	hexane	51–52	$C_{26}H_{35}N_3O_6$
12	71	hexane	148–149	$C_{24}H_{30}N_4O_4$
13	86	hexane	120–121	$C_{25}H_{33}N_3O_4$
14	63	hexane	85–86	$C_{26}H_{35}N_3O_4$
15	78	hexane	87–88	$C_{25}H_{32}FN_3O_4$

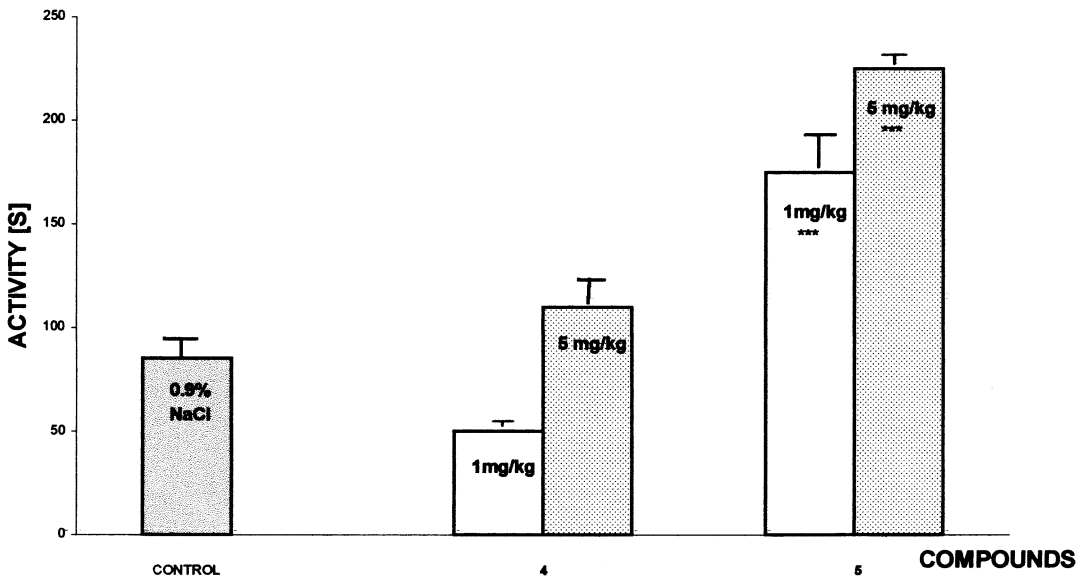


Fig. 1. The effect of compounds **4** and **5** on rat behavior in the Porsolt test. The number of rats in the groups varied from eight to ten. The data are shown as mean ± SEM. *** = $P < 0.001$ related to the control group (saline).

a Varian UNITYplus-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 $\pm 0.5\%$ of the theoretical values. The IR spectra of the compounds showed absorption bands at 1660–1740 cm^{-1} indicating the presence of multiple C=O groups.

*4.1.1. 1-Ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**1**)*

3-Ethoxy-2-cyclohexen-1-one (0.036 mol, 5.0 g), maleimide (0.039 mol, 4.2 g) and 50 mg of *p*-toluenesulfonic acid were refluxed for 20 h with 15 ml of isopropenyl acetate. The solvent was removed in a rotary evaporator. The residue was crystallized from ethyl acetate. In this reaction we obtained two compounds. The mixture of these compounds was refluxed in ethanol and 30% ammonia for 1 h. The residue was crystallized from ethyl acetate to give compound **1**.

^{1}H NMR ($CDCl_3$): 3.71 (m, 1H); 3.57 (m, 1H); 3.36 (dd, $J_1 = 9.8$ Hz, $J_2 = 2$ Hz, 1H, C2–H); 3.22 (dd, $J_1 = 9.8$ Hz, $J_2 = 3.4$ Hz, 1H, C3–H); 2.86 (dd, $J_1 = 8$ Hz, $J_2 = 1$ Hz, 1H, C4–H); 2.49 (dd, $J_1 = 7.2$ Hz, $J_2 = 1.8$ Hz, 2H); 2.14–1.67 (m, 4H).

*4.1.2. General method of preparing N-(4-chlorobutyl)- or (3-bromopropyl)-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**2** and **3**)*

A mixture of 0.03 mol (8 g) 1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**1**) and 0.04 mol (7.23 g) of 1-bromo-4-chlorobutane or 0.1 mol (21.27 g) of 1,3-dibromopropane in 70 ml of ethylmethylketone was refluxed in the presence of 8 g of K_2CO_3 for 51 h. The hot mixture was filtered and the solvent was removed in a rotary evaporator. The residue was crystallized from hexane to give compounds **2** or **3**.

For **2**: ^{1}H NMR ($CDCl_3$): 3.76 (m, 1H); 3.56 (m, 5H); 3.31 (dd, $J_1 = 9.6$ Hz, $J_2 = 2.4$ Hz, 1H, C2–H); 3.16 (dd, $J_1 = 9.6$ Hz, $J_2 = 3.4$ Hz, 1H, C3–H); 2.85 (dd, $J_1 = 4.3$ Hz, $J_2 = 4.3$ Hz, 1H, C4–H); 2.51 (dd, $J_1 = 19.4$ Hz, $J_2 = 2.2$ Hz, 1H); 2.25 (dd, $J_1 = 19.4$ Hz, $J_2 = 2.8$ Hz, 1H); 2.03 (m, 4H); 1.83–1.67 (m, 4H); 1.28 (t, $J = 6.8$ Hz).

*4.1.3. General method of preparing N-[4(4-aryl-1-piperazinyl)butyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**4**–**9**) and N-[3(4-aryl-1-piperazinyl)propyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**10**–**15**)*

Compound **2** or **3** (0.03 mol), 0.003 mol of the appropriate amine, 1 g of anhydrous K_2CO_3 and 0.2 g of KI in 40 ml of acetonitrile were refluxed for 35 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**.

*4.1.3.1. N-[4(4-Pyrimidinyl-1-piperazinyl)butyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**4**).* ^{1}H NMR (DMSO-d_6): 8.44 (d, $J = 4.8$ Hz, 2H); 6.77 (dd, $J_1 = 4.6$ Hz, $J_2 = 4.6$ Hz, 1H); 4.70 (bs, 1H); 4.63 (bs, 1H); 3.70 (m, 2H); 3.45 (m, 10H); 3.04 (m, 5H); 2.16–1.45 (m, 10H); 1.13 (m, 3H).

*4.1.3.2. N-[4(4-Methoxyphenyl-1-piperazinyl)butyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**5**).* ^{1}H NMR ($CDCl_3$): 8.04 (m, 1H); 7.41 (m, 1H); 7.04 (m, 2H); 4.21 (m, 2H); 3.81–3.43 (m, 8H); 3.15 (m, 4H); 3.02 (m, 2H); 2.50 (m, 1H); 2.27–1.53 (m, 4H).

*4.1.3.3. N-[4(4-Pyridyl-1-piperazinyl)butyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**6**).* ^{1}H NMR ($CDCl_3$): 8.18 (dd, $J_1 = 5$ Hz, $J_2 = 1.2$ Hz, 1H); 7.47 (m, 2H); 6.62 (m, 2H); 3.76 (m, 1H); 3.55 (m, 7H); 3.30 (dd, $J_1 = 9.6$ Hz, $J_2 = 2$ Hz, 1H, C2–H); 3.15 (dd, $J_1 = 9.6$ Hz, $J_2 = 3.4$ Hz, C3–H); 2.86 (dd, $J_1 = 4.2$ Hz, $J_2 = 4.2$ Hz, 1H, C4–H); 2.54 (m, 4H); 2.38 (m, 2H); 2.21–1.68 (m, 8H); 1.28 (t, $J = 7$ Hz, 3H).

*4.1.3.4. N-[4(4-Phenyl-1-piperazinyl)butyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**7**).* ^{1}H NMR ($CDCl_3$): 7.26 (m, 2H); 6.88 (m, 3H); 3.76 (m, 1H); 3.55 (m, 3H); 3.29 (dd, $J_1 = 9.8$ Hz, $J_2 = 2$ Hz, 1H, C2–H); 3.19 (m, 5H); 2.86 (dd, $J_1 = 4.2$ Hz, $J_2 = 4.2$ Hz, 1H, C4–H); 2.58 (m, 4H); 2.46–1.93 (m, 8H); 1.52 (m, 4H); 1.28 (t, $J = 7$ Hz, 3H).

*4.1.3.5. N-[4(4-Benzyl-1-piperazinyl)butyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**8**).* ^{1}H NMR ($CDCl_3$): 7.30 (m, 5H); 3.75 (m, 1H); 3.53 (m, 5H); 3.29 (dd, $J_1 = 9.8$ Hz, $J_2 = 2.2$ Hz, 1H, C2–H); 3.14 (dd, $J_1 = 9.8$ Hz, $J_2 = 3.2$ Hz, 1H, C3–H); 2.84 (m, 1H); 2.56–2.43 (m, 6H); 2.33 (m, 4H); 2.19–1.46 (m, 6H); 1.28 (m, 3H).

*4.1.3.6. N-[4(4-Fluorophenyl-1-piperazinyl)butyl]-1-ethoxybicyclo[2.2.2]-oct-5-one-2,3-dicarboximide (**9**).* ^{1}H NMR ($CDCl_3$): 7.00–6.83 (m, 4H); 3.76 (m, 1H); 3.63–3.47 (m, 3H); 3.29 (dd, $J_1 = 9.8$ Hz, $J_2 = 2$ Hz, 1H, C2–H); 3.14 (m, 5H); 2.86 (dd, $J_1 = 3.4$ Hz, $J_2 = 3.4$ Hz, 1H, C4–H); 2.58 (m, 4H); 2.46–1.94 (m, 8H); 1.53 (m, 4H); 1.28 (t, $J = 6.9$ Hz, 3H).

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