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Synthesis of *N,N'*-bis-substituted diimides related to tricyclo[6.2.2.0^{1,6}]dodecane with an expected activity on the central nervous system

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Abstract

Continuing our studies connected with the design of antipsychotic and anxiolytic agents with a reduced propensity toward extrapyramidal side-effects, the synthesis of new compounds related to 3,7-dimethyltricyclo[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxydiimide was performed. The first result of the pharmacological screening test of two of synthesized compounds displayed their low affinity for the serotonin receptor site.

Keywords: Tricyclo[6.2.2.0^{1,6}]dodecane

1. Introduction

Synthesized about ten years ago, a pharmacologically active compound combining anxiolytic and antipsychotic action, umespirone, displays affinities for the 5-HT$_{1A}$ and 5-HT$_2$ receptor sites [1,2].

Umespirone analogs, *N,N'*-bis(4-aryl-1-piperazinylbutyl)-1,8-dimethyl-bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxydiimides synthesized earlier in our department, displayed expected 5-HT$_{1A}$ receptor affinity comparable with that of buspirone. Those compounds were also active in behavioral tests and displayed expected anxiolytic activity [3].

We have later obtained *N,N'*-bis(4-aryl-1-piperazinylbutyl)bicyclo[2.2.2]oct-7-ene-2,3,5,6-tetracarboxydiimides. In pharmacological tests these compounds display only a very low affinity for the 5-HT$_{1A}$ receptor site [4]. This may suggest that the presence of hydrophobic groups in the bicyclic ring system increases the 5-HT$_{1A}$ receptor affinity of the tested compounds and, possibly, their anxiolytic activity.

Continuing our program connected with discovering antipsychotic and anxiolytic agents with a reduced propensity toward extrapyramidal side-effects, we have designed new *N,N'*-bis(4-aryl-1-piperazinylalkyl)polycyclic diimides related to tricyclo[6.2.2.0^{1,6}]dodecane.

2. Chemistry

The desired compounds were synthesized by two routes (Scheme 1).

The starting compound was 3,7-dimethyltricyclo-[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxylic acid dianhydride **1** which was obtained from pulegone and maleic anhydride in the Diels-Alder reaction [5]. In method I, *N,N'*-bis(3-aminopropyl)- and *N,N'*-bis(2-aminoethyl)-substituted derivatives of 3,7-dimethyltricyclo[6.2.2.0^{1,6}]-dodecen-6-yl-9,10,11,12-tetracarboxydiimide described in Table 1 (compounds **4–6** and **8**) were prepared by the condensation of the dianhydride **1** and the appropriate amine (Scheme 1).

The yield of this method was rather low (about 20%), so we were searching for a more effective way to synthesize the designed compounds. Initially we tried to transform dianhydride **1** into diimide by heating in 25% ammonia, but this method, very effective for previous diimides synthesized in our department [2,3], gave no result. Afterwards we tried to obtain 3,7-dimethyltricyclo[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxydiimide **2** by heating dianhydride **1** with anhydrous ammonium carbonate. The diimide **2** obtained in this reaction was very hard to separate from the resulting mixture of mono- and diimides, even by chromatography. A further process, heating in 25% ammonia at 100°C under increased pressure, gave the expected compound

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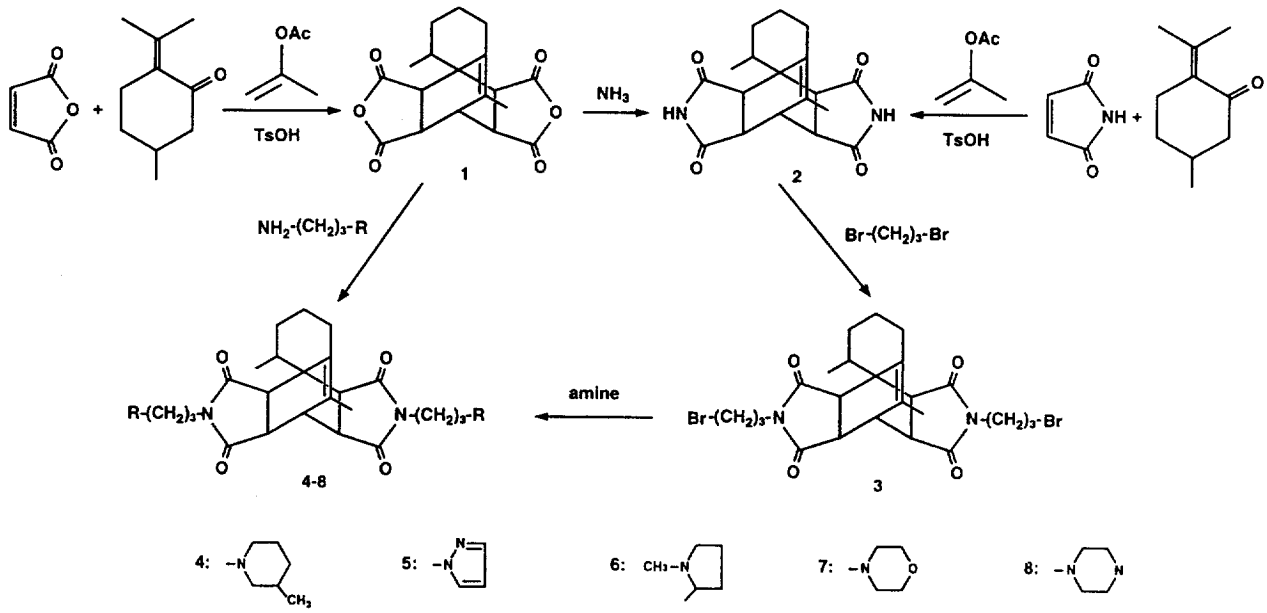
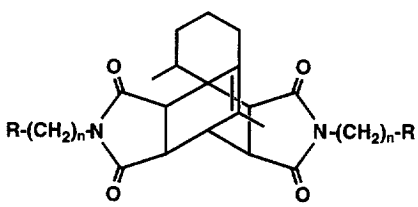
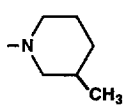
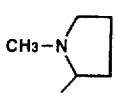
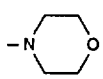
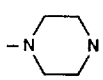


Scheme 1. Routes for synthesizing compounds **4–8**.

Table 1
Physical constants and analytical data of new compounds **3–8**



Comp.	R	*n*	Formula Mol. wt.	M.p. (°C) Solvent	Yield (%)	IR (Nujol) (cm^{-1})
2	H	0	$C_{18}H_{20}N_2O_4 \cdot 2H_2O$ 328.4	>300 isopropanol	40–60	C=O 1695, 1760
3	Br	3	$C_{24}H_{30}N_2O_4Br_2$ 410.5	130–132 heptane	50	C=O 1685, 1750
4		3	$C_{36}H_{54}N_4O_4 \cdot 2H_2O$ 642.9	132–134 acetone/methanol (1:1)	18	C=O 1660, 1695
5		3	$C_{30}H_{36}N_6O_4 \cdot H_2O$ 461.51	126–128 acetone/methanol (1:1)	25	C=O 1650, 1680
6		2	$C_{32}H_{48}N_4O_4 \cdot 2H_2O$ 588.8	129–130 isopropanol	30	C=O 1660, 1690
7		3	$C_{32}H_{46}N_4O_6 \cdot 3H_2O$ 684.8	78–80 isopropanol	30	C=O 1640–1680
8		2	$C_{32}H_{48}N_4O_4 \cdot 2H_2O$ 588.8	135–137 acetone/methanol (1:1)	25	C=O 1720, 1660

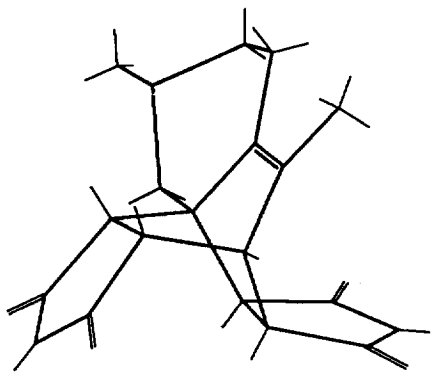


Fig. 1. Structure of 3,7-dimethyltricyclo[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxydiimide **2** (Hyperchem 3).

2 with a yield of about 40%. The last method, involving condensation of maleimide with pulegone in isopropenyl acetate (Diels-Alder reaction), gave the imide **2** with a yield of about 60%.

Method II for the synthesis of *N,N'*-bis-substituted diimides involved alkylation of diimide **2** with 1,3-dibromopropane. The obtained *N,N'*-bis(3-bromopropyl)-3,7-dimethyltricyclo[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxydiimide was condensed with the appropriate amine forming *N,N'*-bis-substituted diimide **7**. The yield of method II was, in general, rather low. The low yield in all methods of synthesis of *N,N'*-bis-substituted 3,7-dimethyltricyclo-[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxydiimides is probably connected with the steric structure of these compounds (Fig. 1).

The spectral data for all the new compounds are consistent with the assigned structures. ^{1}H NMR spectra contain the characteristic signal of protons of the $-CH_3$ group established at 0.9–1.1 ppm (d) and the signal of the $=C-CH_3$ group at about 1.51 ppm (d). The signals of protons of the $-CH_2-$ and –CH– groups in the tricyclic ring system are established at 2.0–2.4 and 2.6–3.2 ppm (broad m and distorted AB-type quartet).

3. Pharmacology

The free bases **5** and **7** were transformed into tetrahydrochlorides and as such subjected to a preliminary pharmacological assay. In the method described by Pazos et al. in Section 4.2.1, both tested compounds displayed only a very low affinity for the 5-HT$_{1A}$ receptor. Less than 50% of the marked ligand, [^{3}H] 8-OH-DPAT, was displaced at the high concentration of 10^{-4} M.

Nevertheless, since the relationship between the affinity of a compound for the 5-HT$_{1A}$ receptor and its anxiolytic activity is not well documented, the new compounds will be tested for anxiolytic activity in a behavioral test.

4. Experimental

4.1. Chemistry

Melting points were determined on a Kofler apparatus and are uncorrected. IR spectra were recorded on a Specord 75 IR spectrophotometer (Zeiss, Jena, Germany) in KBr pellets; ^{1}H NMR spectra were recorded with a Tesla 567A 100 MHz apparatus, with tetramethylsilane (TMS) as internal reference. Elemental analyses (C, H, N) were within ±0.4% of theoretical values.

*4.1.1. Synthesis of N,N'-bis(3-aminopropyl)- and N,N'-bis(2-aminoethyl)-3,7-dimethyltricyclo[6.2.2.0^{1,6}]-dodecen-6-yl-9,10,11,12-tetracarboxydiimides **4–6***

A solution of 0.024 mol of the appropriate amine in 5 ml of acetone was added dropwise to a solution of 0.008 mol (2.64 g) of dianhydride **1** in 30 ml of acetone. The precipitate formed was filtered and recrystallized from the appropriate solvent (Table 1).

4.1.2. Synthesis of 3,7-dimethyltricyclo[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxydiimide 2

0.004 mol (1.32 g) of dianhydride **1** in 60 ml of 25% ammonia solution was heated for 1 h at 100°C in an autoclave of volume 100 cm^3. The solid formed was filtered after cooling and crystallized from 50% ethanol solution to give **2**.

Method II: 0.02 mol (3 g) of pulegone, 0.05 mol (4.5 g) of maleimide, and 0.001 g of *p*-toluenesulfonic acid in 15 cm^3 of isopropenyl acetate were refluxed for 50 h. The solvent was distilled off and the residue was crystallized from isopropanol yielding **2**.

4.1.3. Synthesis of N,N'-bis(3-bromopropyl)-3,7-dimethyltricyclo[6.2.2.0^{1,6}]dodecen-6-yl-9,10,11,12-tetracarboxydiimide 3

A mixture of 0.008 mol (2.6 g) of diimide **2** and 0.1 mol (21.5 g) of 1,3-dibromopropane in 100 cm^3 of ethyl acetate was refluxed in the presence of 15 g K_2CO_3 for 100 h. The hot mixture was filtered and the solvent was removed in a rotary evaporator. The residue was crystallized from heptane.

4.1.4. N,N'-bis(3-morpholinepropyl)-3,7-dimethyltricyclo[6.2.2.0^{1,6}]dodecen-6-yl-9,10,1,12-tetracarboxydiimide 7

0.0025 mol (1.4 g) of compound **3**, 0.05 mole (9.7 g) of morpholine and 0.04 mol (5.52 g) of potassium carbonate in 100 cm^3 of acetone were refluxed for 90 h. The hot mixture was filtered and the solvent was removed in a rotary evaporator. The oily residue was crystallized from isopropanol.

4.2. Pharmacology

4.2.1. Receptor binding determinations

The binding reaction was performed according to the method described by Pazos et al. [6] using anterior parts of

the rat brain stem and [^{3}H] 8-OH-DPAT (specific activity 183 Ci/mM) as a specific ligand for serotonin (5-HT_{1A}) receptors. The compounds were tested at concentrations ranging from 3×10^{-10} to 3×10^{-3} M. Samples were counted on a Betamatic II (scintillating Kontron β-counter). Results generally are expressed as mean values of at least five independent experiments as pK_i (affinity constant; $-\log K_i$ mol/l) calculated according to the program set up by Munson [7] using an IBM PC machine. Both tested compounds displaced only about 50% of the marked ligand ([^{3}H] 8-OH-DPAT) at a concentration of 10^{-4} M. Because of the very low affinity for the 5-HT_{1A} receptor, the factors B_{max}, K_D and K_i were not calculated for these compounds.

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