ANNALES
UNIVERSITATIS MARIAE CURIE-SKŁODOWSKA
LUBLIN – POLONIA

VOL. LVIII, 12 SECTIO AA 2003

Synthesis of new N-substituted cyclic imides with an expected anxiolytic activity.xxvi.derivatives of N-hydroxy-7-diphenylmethylenebicyclo[2.2.1]hept--2-ene-5,6-dicarboximide

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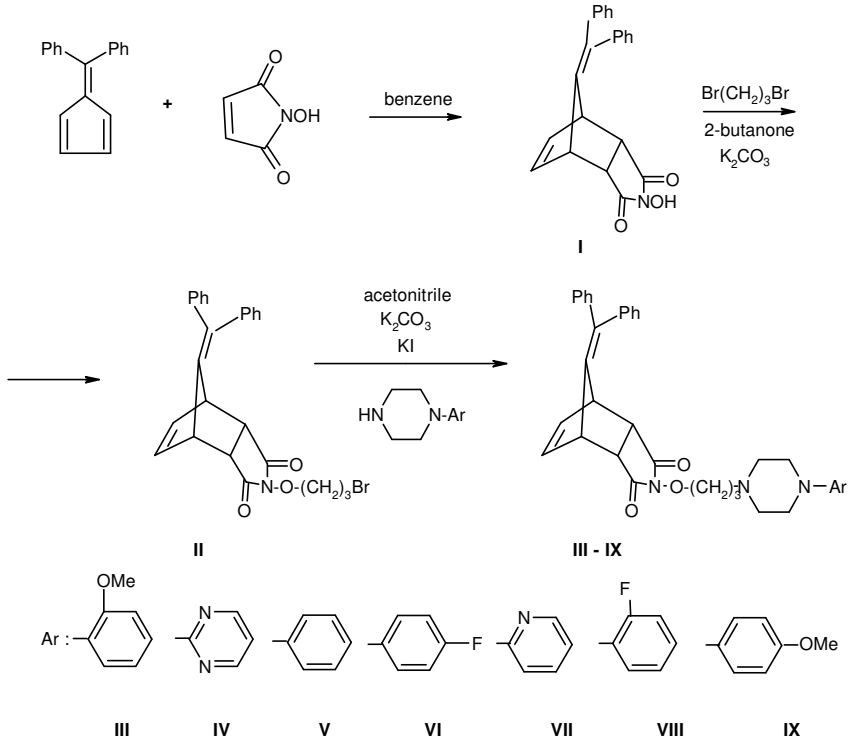
This paper presents the methods used for preparation of new *N*-substituted derivatives of N-hydroksy-7- diphenylmethylenebicyclo[2.2.1]hept-2-ene-5,6-dicarboximide. The starting material was N-hydroxy-7-diphenyl-methylenebicyclo[2.2.1]hept-2-ene-5,6-dicarboximide.

1. INTRODUCTION

The behaviour of activity of some anxiolytics suggest as being based mainly on an interaction with serotonin $5HT_{1A}$ receptor [1]. N-substituted arylpiperazines produce a variety of behavioural responses and pharmacological effects due to activation of the central serotonin system [2,3]. As a result of these studies and in search of new chemical compounds possessing an expected anxiolytic activity among bicyclic N-substituted arylpiperazines, known as ligands of the $5HT_{1A}$ receptor [4-6], a series of derivatives of N-hydroxy-7-diphenylmethylenebicyclo[2.2.1]hept-2-ene-5,6-dicarboximide were prepared.

The starting material for the synthesis of the desired compounds was N-hydroxy-7-diphenylmethylenebicyclo[2.2.1]hept-2-ene-5,6-dicarboximide **I**, that was obtained in Diels-Alder reaction of 6,6-diphenylfulvene with N-hydroxymaleimide. By alkylation of the imide **I** with 1,3-dibromopropane, N-(3-bromopropyl) substituted derivative **II** was obtained. Next the compound **II** was condensed with appropriate amines.

The structures of new derivatives of imide **I** have been established on the basis of ^{1}H NMR and elemental analysis (Table 1).



Tab. 1. Physical, analytical and ^{1}H NMR spectral data of compounds [**I**-**IX**]

Comp. No	Formula molecular weight	Solvent m.p. [^{O}C]	Yield %	Analysis Calculated/found %C	%H	%N	^{1}H NMR, δ (ppm) 200 MHz, $CDCl_3$
I	$C_{22}H_{17}NO_3$ 343	benzene 211-212	85	76.97 76.80	4.97 5.25	4.08 3.95	7.37-7.26(m, 6H, H_{arom}) 7.05(m, 4H, H_{arom}) 6.35(dd, J_1= J_2=1.8 Hz, 2H, C_6,C_5-H) 3.91(m, 2H, C_1-H, C_4-H) 3.41(d, J=1.6 Hz, 1H) 3.39(d, J=1.4 Hz,1H, C_2,C_3-H)

Comp. No	Formula nolecular weight	Solvent m.p. [^{O}C]	Yield %	Analysis Calculated/found %C	%H	%N	^{1}H NMR, δ (ppm) 200 MHz, $CDCl_3$
II	$C_{25}H_{22}NBrO_3$ 464	heptane 159-160	71	64.66 64.76	4.78 4.61	3.02 3.20	7.38-7.24(m, 6H, H_{arom}) 7.06(m, 4H, H_{arom}) 6.42(dd, J_1= J_2=1.8 Hz, 2H, C_6,C_5-H) 4.14(t, 2H, C_1-H, C_4-H) 3.60(t, J=6.4 Hz, 2H) 3.38-3.37(d, J=1.4 Hz, 1H, C_2,C_3-H) 2.19(dt, J=6Hz, 2H, $C_{2'}$-H)
III	$C_{36}H_{37}N_3O_4$ 575	octane 170-171	48	75.13 74.78	6.43 6.43	7.30 8.15	7.36(m, 6H, H_{arom}) 7.09-6.84 (m, 8H, H_{arom}) 6.41(dd, J_1= J_2=2 Hz, 2H, C_6,C_5-H) 4.07(t, 2H, J=6.6 Hz, $C_{1'}$-H) 3.94(m, 2H, C_1-H, C_4-H) 3.38-3.37(s, 1H, C_2, C_3-H) 3.08(m, 4H, piperazine-Φ) 2.65(m, 6H, piperazine, $C_{3'}$-H) 1.90(m, 2H, $C_{2'}$-H)
IV	$C_{33}H_{33}N_5O_3$ 547	hexane 138-139	50	72.39 72.56	6.03 6.07	12.80 12.73	8.30(d, J=4.6 Hz, 2H, H_{α}pyr) 7.35-7.28(m, 6H, H_{arom}) 7.06 (m, 4H, H_{arom}) 6.47(dd, J_1= J_2=4.8 Hz, 1H, H_{β}pyr) 6.41(dd, 2H, J_1= J_2=2.1 Hz, C_6,C_5-H) 4.08(t, J=6.6 Hz, 2H, $C_{1'}$-H,) 3.94(m, 2H, C_1-H, C_4-H) 3.81(t, J=5 Hz,4H, $(CH_2)_2$N-Pyr) 3.38(d, J=1.6 Hz, C_2,C_3-H) 3.36(d, J=1.8 Hz, C_2,C_3-H) 2.52(m, 6H, $C_{3'}$-H, N$(CH_2)_2$) 1.89 (m, 2H, $C_{2'}$-H)

Comp. No	Formula molecular weight	Solvent m.p. [^{O}C]	Yield %	Analysis Calculated/found %C	%H	%N	^{1}H NMR, δ (ppm) 200 MHz, $CDCl_3$
V	$C_{33}H_{33}N_3O_3$ 521	hexane 132-133	54	77.06 76.79	6.42 6.54	7.71 7.82	7.37-7.22 (m, 8H, H_{arom}) 7.06 (m, 4H, H_{arom}) 6.95-6.81(m, 3H, H_{arom}) 6.05(dd, J_1= J_2=2.1 Hz, 2H, C_5,C_6-H) 4.07(t, J=6.4 Hz, 2H, $C_{1'}$-H,) 3.94(m, 2H, C_1-H, C_4-H) 3.37(d, J=1.4 Hz, C_2,C_3-H) 3.36(d, J=1.6 Hz, C_2,C_3-H) 3.19(m, 4H, $N(CH_2)_2$) 2.61(m, 6H, $C_{3'}$-H, $N(CH_2)_2$) 1.89 (m, 2H, $C_{2'}$-H)
VI	$C_{33}H_{34}N_3FO_3$ 539	hexane 143.5-144	53	74.60 74.63	6.04 5.24	7.46 7.59	7.53-7.28 (m, 6H, H_{arom}) 7.08-6.83 (m, 8H, H_{arom}) 6.41(dd, J_1= J_2=2.2 Hz, 2H, C_5,C_6-H) 4.07(t, J=6.2 Hz, 2H, $C_{1'}$-H,) 3.94(m, 2H, C_1-H, C_4-H) 3.38 (d, J=1.6 Hz, C_2,C_3-H) 3.36(d, J=1.8 Hz, C_2-H, C_3-H) 3.11(m, 4H, $N(CH_2)_2$) 2.61(m, 6H, $C_{3'}$-H, $N(CH_2)_2$) 1.89 (m, 2H, $C_{2'}$-H)

Comp. No	Formula molecular weight	Solvent m.p. [^{O}C]	Yield %	Analysis Calculated/found %C	%H	%N	^{1}H NMR, δ (ppm) 200 MHz, $CDCl_3$
VII	$C_{32}H_{34}N_4O_3$ 522	hexane 144-145	55	74.72 74.25	6.23 6.25	10.26 10.19	8.18 (m, 1H, H_{α}pyr) 7.51-7.28 (m,) 7.06 (m, 5H) 6.62(m, 2H, H_{β}pyr) 6.41(dd, J_1= J_2=2.2 Hz, 2H, C_5,C_6-H) 4.08(t, J=6.4 Hz, 2H, $C_{1'}$-H,) 3.94(m, 2H, C_1-H, C_4-H) 3.53 (t, J=5.1 Hz, 4H, $N(CH_2)_2$) 3.37(d, J=1.4 Hz, 1H,C_2,C_3-H) 3.36(d, J=1.8 Hz, 1H,C_2,C_3-H) 2.56(t, J=5.1 Hz, 6H, $C_{3'}$-H, $N(CH_2)_2$) 1.90 (m, 2H, $C_{2'}$-H)
VIII	$C_{33}H_{34}N_3FO_3$ X 1.75 H_2O 570.5	121-122	48	74.64 74.58	6.04 6.01	7.47 7.56	7.33-7.29 (m, 6H, H_{arom}) 7.08-6.87 (m, 8H, H_{arom}) 6.41(dd, J_1= J_2=1.8 Hz, 2H, C_5,C_6-H) 4.08(t, J=6 Hz, 2H, $C_{1'}$-H,) 3.95(m, 2H, C_1-H, C_4-H) 3.37 (d, J=1.4 Hz, 1H, C_2-H, C_3-H) 3.38(d, J=1.4 Hz, 1H, C_2-H, C_3-H) 3.11(m, 4H, $N(CH_2)_2$ -Φ) 2.67-2.56(m, 6H, $N(CH_2)_2$) 1.90 (m, 2H, $C_{2'}$-H)

IX	$C_{36}H_{37}N_3O_4$ X 5/3 H_2O 605	hexane 158-159	50	75.39 75.17	6.45 6.38	7.33 7.54	7.37-7.28 (m, 6H, H_{arom}) 7.08-7.03 (m, 4H, H_{arom}) 6.93-6.80 (m, 4H, H_{arom}) 6.41(dd, J_1= J_2=1.8 Hz, 2H, C_5,C_6-H) 4.08(t, J=6 Hz, 2H, $C_{1'}$-H,) 3.94(m, 2H, C_1-H, C_4-H) 3.77 (s, 3H, OCH_3) 3.37(d, J=1.4 Hz, 1H, C_2-H, C_3-H) 3.38(d, J=1.4 Hz, 1H, C_2-H, C_3-H) 3.11(m, 4H, $N(CH_2)_2$ -Φ) 2.65(m, 4H, $N(CH_2)_2$) 1.92 (m, 2H, $C_{2'}$-H)

2. EXPERIMENTAL

Melting points were determined in a capillary in Electrothermal 9100 apparatus and are uncorrected. Nuclear magnetic resonance spectra for proton (^{1}H NMR) were recorded on a 200 MHz spectrometer- UNITY plus 200, VARIAN's apparatus in $CDCl_3$.

The chemical shift values are expressed in ppm (parts per milion) relative to tetramethylsilane as an internal standard.

N-HYDROKSY-7-DIPHENYLMETHYLENEBICYCLO[2.2.1]HEPT-2-ENE-5,6-DICARBOXIMIDE I

A mixture of 6,6-diphenylfulvene (5 g, 20 mmol) and N-hydroksymaleimide (2.2 g, 19.5 mmol) in benzene (20 ml) was refluxed for 1.5 h. The solvent was evaporated and the residue was crystallized from benzene.

N-(3-BROMOprOPYL)-N-HyDROXY-7-DIPHENYLMETHYLENE-BICYCLO [2.2.1]HEPT-2-ENE-5,6-DICARBOXIMIDE II

A mixture of imide **I** (4 g, 12 mmol), 1,3-dibromopropane (11.7 g, 58 mmol) and anhydrous K_2CO_3 (4.02 g, 29 mmol) in 2-butanone (100 ml) was refluxed for 40 h. The inorganic precipitate was filtered off, the solvent was evaporated. Compound **II** was crystallized from heptane.

GENERAL PROCEDURE FOR PREPARING OF N-[3-(4-ARYL-1-PIPERAZINYL) PROPYL]-N-Hydroxy-7-DIPHENYLMETHYLENE BICYCLO [2.2.1] HEPT-2-ENE-5,6-DICARBOXIMIDE

A mixture of the compound **II** (2 mmol), anhydrous K_2CO_3 (0.3 g, 2 mmol), KI (0.2 g, 1 mmol) and the corresponding *N*-substituted piperazine (4 mmol), was refluxed in acetonitrile (50 ml) for 30-40 h. When the reaction was complete by TLC (silica gel, developing system:chloroform-methanol) the mixture was filtered and the solvent was evaporated. The residue was crystallized from appropriate solvent to give compounds **IV**-**VII**, **IX** or purified by column chromatography (compounds **III** and **VIII**) (Table 1).

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CURRICULUM VITAE

Aneta Prędka was born in Sosnowiec in 1977. In 1992 she was graduated from secondary school in Sosnowiec. In 1996 she began studies in the Chemistry Department of Warsaw University. In 2001 she obtained M.A. degree in Chemistry. Since 2001 she worked in The Chair and Department of Medical Chemistry, The Medical University of Warsaw. Fields of interest: organic synthesis, synthesis of anxiolytic, antidepressive and β-adrenolytic compounds. During the time she presented 2 posters.