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Synthesis of new N-substituted cyclic imides with an expected anxiolytic activity. XXVII. Derivatives of 1-chloromethyl-dibenzo[e.h]bicyclo[2.2.2] octane-2,3-dicarboximide

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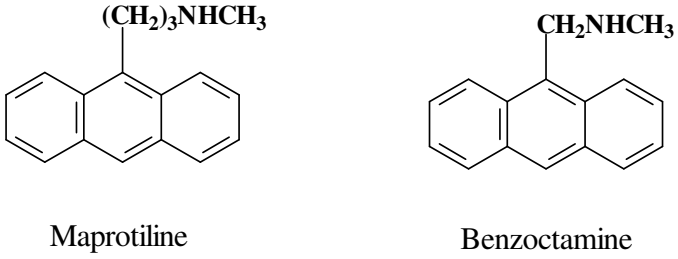
This paper presents the preparation of a number of new derivatives of 1-chloromethyl-dibenzo[e.h]bicyclo[2.2.2]-octane-2,3-dicarboximide with an expected anxiolytic activity.

1. INTRODUCTION

Anxiolytic drugs without side effects are still being sought. New kinds of drugs from this group, without benzodiazepine-related side effects, such as: addiction, drowsiness, convulsion, muscle relaxation, are derivatives of buspirone, which demonstrate efficiency similar to diazepam. During the last few years it has been reported, that some derivatives of certain cyclic imides which possess 4-aryl (heteroaryl)-1-piperazinealkyl group linked with the imide nitrogen produce activation of the central serotonin system [1,2] and have anxiolytic or antidepressive activity [3,4].

Maprotiline and benzoctamine, drugs derived from anthracene, present anxiolytic and antidepressive activity [5].

Looking for a new group of anxiolytic drugs we decided to link the anthracene system of Maprotiline or Benzoctamine with 4-aryl(heteroaryl)-1-piperazinealkyl group to achieve better activity. The 4-aryl(heteroaryl)-1-piperazinealkyl group is a part of a molecule of buspirone and it is considered to be responsible for pharmacological activity.



Maprotiline Benzoctamine

Fig. 1

Looking for a new group of anxiolytic drugs we decided to link the anthracene system of Maprotiline or Benzoctamine with 4-aryl(heteroaryl)-1-piperazinealkyl group to achieve better activity. The 4-aryl(heteroaryl)-1-piperazinealkyl group is a part of a molecule of buspirone and it is considered to be responsible for pharmacological activity.

Previously we described the syntheses of cyclic imides [6,7,8] and their derivatives.

As a result of our studies, we decided to present the syntheses of *N*-substituted derivatives of 1-chloromethyl-dibenzo[e.h]bicyclo[2.2.2]octane-2.3-dicarboximide (Fig.2).

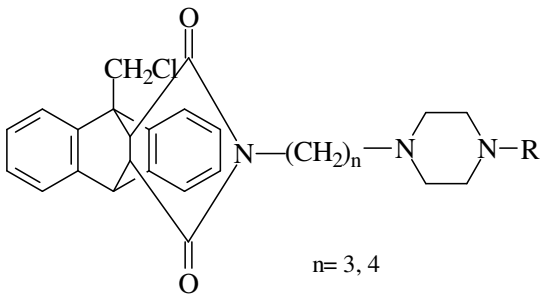
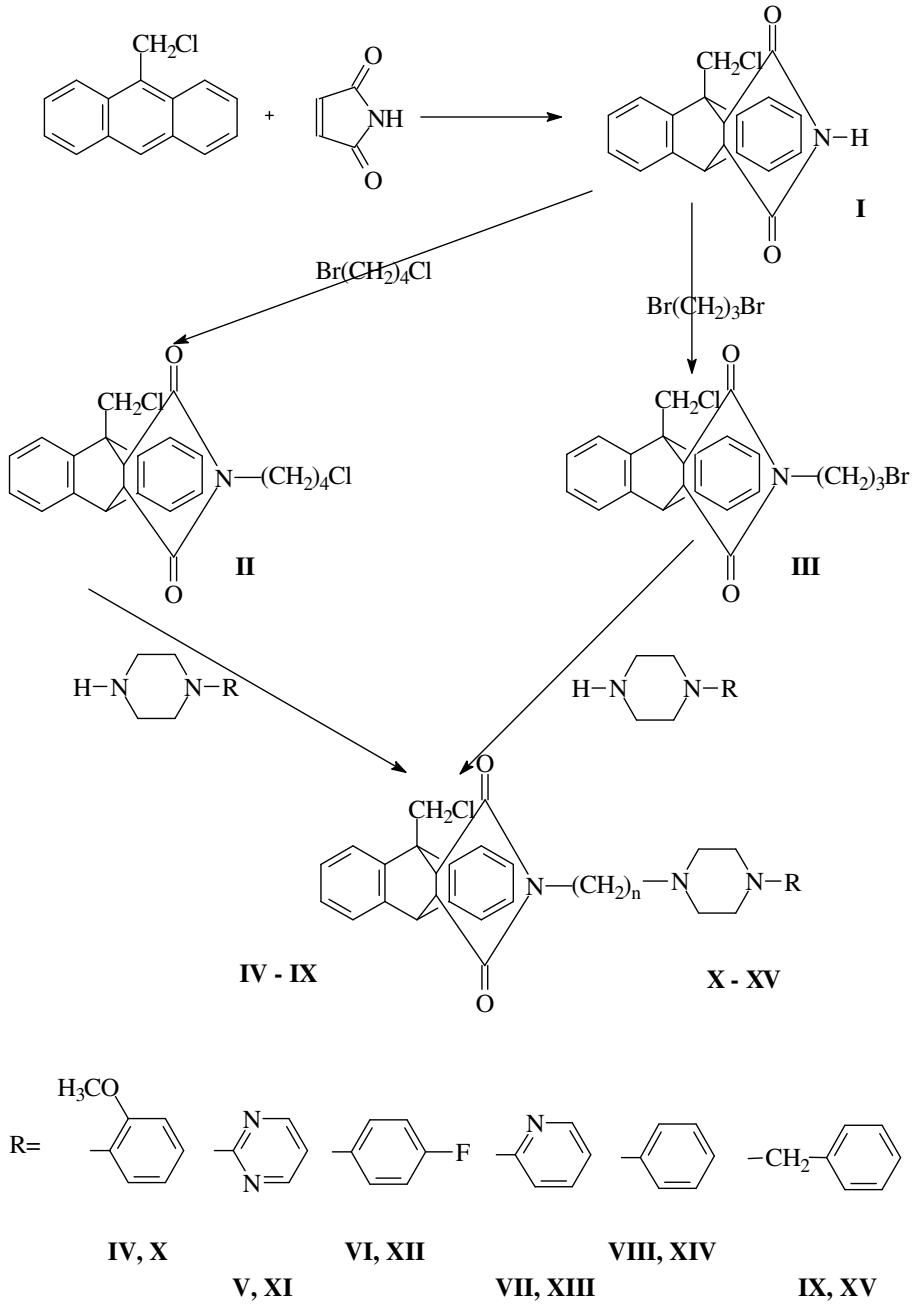


Fig. 2

Imide **I** (Scheme 1), obtained in Diels-Alder reaction of 9-chloromethyl-anthracene and maleimide, was used as an initial compound. It was refluxed with 1,3-dibromopropane or 1-bromo-4-chlorobutane in acetonitrile in a presence of anhydrous K_2CO_3 to give *N*-(3-bromopropyl)- **III** or N-(4-chlorobutyl)-substituted imide **II**, which was condensed with appropriate arylpiperazines. The structures of the new derivatives of imide **I** were confirmed by elemental analysis, IR and ^{1}H NMR spectra (Table 1).


CH2Cl
NH
O
N−H
I
Br(CH2)4Cl
Br(CH2)3Br
N—(CH2)4Cl
N—(CH2)3Br
II
III
H−N
N−R
N—(CH2)n—N
IV - IX
X - XV
R=
H3CO
F
−CH2−
IV, X
V, XI
VI, XII
VII, XIII
VIII, XIV
IX, XV

Scheme 1

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

Comp. no	Formula molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calc/Found . %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
I	$C_{19}H_{14}NO_2Cl$ 323,78	Ethyl acetate 285-286	95	70,48 70,38	4,36 4,56	4,32 4,19	10.87 (s, 1H, NH), 7.60 (m, 1H, H_{arom}), 7.48 (m, 1H, H_{arom}), 7.36-7.17 (m, 6H, H_{arom}), 5.09 (m, 2H, -C1-CH_2), 4.72 (d, J=3 Hz, 1H, H_a), 3.38 (m, 2H, H_b, H_c)
II	$C_{23}H_{21}NO_2BrCl$ 458,78	octane 203-204	64	60,21 59,93	4,61 4,61	3,08 3,08	7.68 (m, 1H, H_{arom}), 7.41-7.17 (m, 7H, H_{arom}), 5.14 (br.s., 1H, -C1-CH_2), 4.87 (br.s., 1H, -C1-CH_2), 4.76 (d, J=2.8 Hz, 1H, H_a), 3.53 (br.s., 1H, H_b), 3.28 (dd, J_1=8.8 Hz, J_2=3.0 Hz,, 1H, H_c), 3.15 (t, J=6.6 Hz, 4H, C1'-H, C4'-H), 1.20 (m, 2H, C3'-H), 1.0 (m, 2H, C2'-H).
IV	$C_{34}H_{36}N_3O_3Cl$ *0,2 H_2O 573,74	hexane 103-104	72	71,17 71,14	6,39 6,06	7,32 7,19	7.68 (d, J=6.6 Hz, 1H, H_{arom}), 7.41-7.15 (m, 7H, H_{arom}), 7.04-6.84 (m, 4H, H_{arom}), 5.16 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.76 (d, J=3.0 Hz, 1H, H_a), 3.27 (dd, J_1=8.6 Hz, J_2=3.0 Hz, 1H, H_b) 3.10 (m, 6H, C1'-H, H_c, $(CH_2)_2$-Nϕ), 2.57 (m, 4H, N-$(CH_2)_2$), 2.21 (t, J=7.6 Hz, 2H, C4'-H), 1.14 (m, 2H, C2'-H) 0.84 (m, 4H, C3'-H).

Comp. no	Formula molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calc/Found . %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
V	$C_{31}H_{32}N_5O_2Cl$ *0,25 H_2O 546,60	octane 170-171	92	68,12 68,10	5,99 6,01	12,81 12,81	8.30 (d, J=4.8 Hz, 2H, H_{α}-pyr), 7.69 (m, 1H, H_{arom}), 7.41-7.14 (m, 7H, H_{arom}), 6.47 (dd, J_1= J_2=4.6 Hz, 1H, H_{β}-pyr), 5.17 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.76 (d, J=3.2 Hz, 1H, H_a), 3.80 (t, J=5.1 Hz , 4H, $(CH_2)_2$-Nϕ), 3.46 (br.s., 1H, H_b), 3.28 (dd, J_1=8.4 Hz, J_2=3.0 Hz, 1H, H_c,), 3.11 (t, J=7.2 Hz, 2H, C1'-H), 2.42 (t, J=5.2 Hz, 4H, $(CH_2)_2$-N) 2.17 (t, J=7.2Hz, 2H,C4'-H), 1.11 (m ,2H, C2'-H), 0.85 (m, 2H, C3'-H).
VI	$C_{33}H_{33}N_2O_3ClF$ 558,11	octane 198-199	82	71,02 70,98	5,96 5,97	7,53 7,54	7.68 (m, 1H, H_{arom}), 7.41-7.14 (m, 7H, H_{arom}), 7.00-6.83 (m, 4H, H_{arom}), 5.16 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.75 (d, J=3.2 Hz, 1H, H_a), 3.52 (m, 1H, H_b), 3.27 (dd, J1=8.4Hz, J2=3.2 Hz, 1H, H_c), 3.10 (m, 6H, C1'-H, $(CH_2)_2$-Nϕ), 2.52 (t, J=5.2 Hz, 4H, $(CH_2)_2$-N), 2.19 (t, J=7.3Hz, 2H,C4'-H), 1.11 (m, 2H, C2'-H), 0.85 (m, 2H, C3'-H).

Comp. no	Formula molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calc/Found . %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
VII	$C_{32}H_{33}N_4O_2Cl$ 541,11	hexane 189-190	52	71,03 70,64	6,15 6,11	10,36 10,20	8.18 (dd, J_1=5.0 Hz, J_2=1.8 Hz, 1H, H_{α}-pyr), 7.68 (m, 1H, H_{arom}), 7.51-7.14 (m, 8H, H_{arom}), 6.62 (m, 2H, H_{β}-pyr), 5.16 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.76 (d, J=3.2 Hz, 1H, H_a), 3.52 (t, J=5.0 Hz, 4H, $(CH_2)_2$-Nϕ), 3.27 (d, J1=8.4 Hz, J2=3.2 Hz, 1H, H_c), 3.11 (t, J=7.1Hz, 2H,C1'-H), 2.47 (t, J=5.4 Hz, 4H, $(CH_2)_2$-N), 2.18 (t, J=7.4Hz, 2H, C4'-H) 1.12 (m, 2H, C2'-H), 0.85 (m, 2H, C3'-H)
VIII	$C_{33}H_{34}N_3O_2Cl$ 540,12	hexane 196-197	53	73,38 73,18	6,34 6,23	7,78 7,74	7.68 (d, J=6.6Hz, 1H, H_{arom}), 7.41-7.14 (m, 9H, H_{arom}), 6.89 (m, 3H, H_{arom}), 5.16 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.75 (d, J=3.2 Hz, 1H, H_a), 3.50 (m, 1H, H_b) 3.28 (dd, J_1=8.4Hz, J_2=3.2 Hz, 1H, H_c) 3.15 (m, 6H, C1'-H, $(CH_2)_2$-Nϕ), 2.53 (t, J=5.2 Hz, 4H, N-$(CH_2)_2$), 2.19 (t, J=7.4Hz, 2H,C4'-H), 1.12 (m, 2H, C2'-H) 0.85 (m, 4H, C3'-H).

Comp. no	Formula molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calc/Found . %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
IX	$C_{34}H_{36}N_3O_2Cl$ 554,14	hexane 186-187	49	73,69 73,81	6,55 6,43	7,58 7,66	7.69 (d, J=7.0Hz, 1H, H_{arom}), 7.41-7.13 (m, 12H, H_{arom}), 6.89 (m, 3H, H_{arom}), 5.14 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.75 (d, J=2.8 Hz, 1H, H_a), 3.50 (m, 3H, H_b, CH_2-ϕ), 3.26 (dd, J_1=8.4Hz, J_2=3.0 Hz, 1H, H_c) 3.07 (t, J=7.4Hz, 2H,C1'-H), 2.42 (m, 8H, H-piperazine), 2.13 (t, J=7.6Hz, 2H,C4'-H), 1.09 (m, 2H, C2'-H) 0.80 (m, 4H, C3'-H).
III	$C_{22}H_{19}NO_2BrCl$ *0,25 H_2O 449,26	octane 241-242	85	58,82 58,86	4,37 4,29	3,12 3,14	7.69 (m, 1H, H_{arom}), 7.42-7.20 (m, 7H, H_{arom}), 5.00 (br.m, 2H, -C1-CH_2), 4.76 (d, J=3.0 Hz, 1H, H_a), 3.28 (m, 4H, H_b, H_c, C1'-H), 2.71 (t, J=7.0 Hz, 2H, C3'-H), 1.40(m, 2H, C2'-H).

Comp. no	Formula molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calc/Found . %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
X	$C_{33}H_{34}N_3O_3Cl$ *0,5 H_2O 565,13	hexane 98-99	62	70,13 69,94	6,24 6,11	7,43 7,06	7.69 (d, J=7.4 Hz, 1H,H_{arom}), 7.41-7.16 (m, 7H, H_{arom}), 7.04-6.83 (m, 4H, H_{arom}), 5.16 (br.s., 1H, -C1-CH_2), 4.85 (br.s., 1H, -C1-CH_2), 4.75 (d, J=2.8 Hz, 1H, H_a), 3.86 (s, 3H, -OCH_3) 3.30 (m, 2H, C1'-H, H_b H_c,), 3.17 (t, J=7.6Hz, 2H,C1'-H), 3.05 (m, 4H, $(CH_2)_2$-Nϕ), 2.50 (m, 4H, N-$(CH_2)_2$), 2.09 (t, J=7.2Hz, 2H,C4'-H) 1.00 (m, 2H, C2'-H).
XI	$C_{30}H_{30}N_5O_2Cl$ *$3H_2O$ 528,07	octane 215-216	63	68,23 67,98	5,73 5,75	13,26 13,26	8.30 (d, J=4.8 Hz, 2H, H_{α}-pyr), 7.69 (d, J=6.8Hz, 1H, H_{arom}), 7.42-7.13 (m, 7H, H_{arom}), 6.48 (dd, J_1= J_2=4.8 Hz, 1H, H_{β}-pyr), 5.17 (br.s., 1H, -C1-CH_2), 4.87 (br.s., 1H, -C1-CH_2), 4.76 (d, J=3.2 Hz, 1H, H_a), 3.78 (t, J=5.0Hz , 4H, $(CH_2)_2$-Nϕ), 3.50 (br.s., 1H, H_b), 3.28 (dd, J_1=8.4 Hz, J_2=3.0 Hz, 1H, H_c,), 3.17 (t, J=7.4 Hz, 2H, C1'-H), 2.34 (t, J=5.2 Hz, 4H, $(CH_2)_2$-N) 2.03 (t, J=7.2Hz, 2H,C3'-H), 0.99 (m ,2H, C2'-H).

Comp. no	Formula molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calc/Found. %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
XII	$C_{32}H_{31}N_3O_2ClF$ 544,08	octane 170-171	57	70,64 70,48	5,74 5,65	7,72 7,90	7.68 (d, J=6.6Hz, 1H, H_{arom}), 7.42-7.15 (m, 6H, H_{arom}), 7.00-6.82 (m, 5H, H_{arom}), 5.18 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.76 (d, J=3.0 Hz, 1H, H_a), 3.74-3.50 (m, 1H, H_b), 3.28 (dd, J1=8.6Hz, J2=3.0 Hz, 1H, H_c), 3.17 (t, J=4Hz, 2H, C1'-H), 3.08 (m, 4H, $(CH_2)_2$-Nϕ), 2.45 (m, 4H, N-$(CH_2)_2$), 2.06 (t, J=7.0Hz, 2H,C3'-H), 0.99 (m, 2H, C2'-H).
XIII	$C_{31}H_{31}N_4O_2Cl$ 527,08	hexane 105-106	73	70,64 70,60	5,93 5,84	10,63 10,76	8.18 (dd, J_1=4.8 Hz, J_2=1.2 Hz, 1H, H_α-pyr), 7.69 (d, J=6.4Hz, 1H, H_{arom}), 7.52-7.13 (m, 8H, H_{arom}), 6.61 (m, 2H, H_β-pyr), 5.17 (br.s., 1H, -C1-CH_2), 4.86 (br.s., 1H, -C1-CH_2), 4.76 (d, J=3.2 Hz, 1H, H_a), 3.50 (m, 4H, $(CH_2)_2$-Nϕ), 3.39 (t, J=5.2Hz,4H, N-$(CH_2)_2$), 3.28 (dd, J_1=8.6 Hz, J2=3.0 Hz, 1H, H_c), 2.05 (t, J=5.4 Hz, 4H, $(CH_2)_2$-N), 2.18 (t, J=7.0Hz, 2H, C3'-H) 0.99 (m, 2H, C2'-H),

Comp. no	Formula molecular weight	Solvent m.p. [^{O}C]	Yield [%]	Analysis Calc/Found . %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
XIV	$C_{32}H_{32}N_3O_2Cl$ 526,09	octane 142-143	72	73,06 72,68	6,13 6,16	7,99 8,02	7.69 (d, J=7.4Hz, 1H, H_{arom}), 7.42-7.15 (m, 9H, H_{arom}), 6.93-6.81 (m, 3H, H_{arom}), 5.18 (br.s., 1H, -C1-CH_2), 4.87 (br.s., 1H, -C1-CH_2), 4.75 (d, J=2.8 Hz, 1H, H_a), 3.52 (m, 1H, H_b) 3.28 (dd, J_1=8.2Hz, J_2=3.2 Hz, 1H, H_c) 3.17 (m, 6H, C1'-H, $(CH_2)_2$-Nϕ), 2.45 (m, 4H, N-$(CH_2)_2$), 2.06 (t, J=7.2Hz, 2H,C3'-H), 1.00 (m, 2H, C2'-H)
XV	$C_{33}H_{34}N_3O_2Cl$ 540,12	hexane 138-139	65	73,38 73,20	6,34 6,25	7,78 7,90	7.68 (d, J=6.6Hz, 1H, H_{arom}), 7.40-7.13 (m, 12H, H_{arom}), 6.89 (m, 3H, H_{arom}), 5.13 (br.s., 1H, -C1-CH_2), 4.83 (br.s., 1H, -C1-CH_2), 4.74 (d, J=3.0 Hz, 1H, H_a), 3.49 (s, 2H, CH_2-ϕ), 3.58-3.39 (m, 1H, H_b), 3.24 (dd, J_1=8.2Hz, J_2=3.2 Hz, 1H, H_c) 3.12 (t, J=7.4Hz, 2H,C1'-H), 2.81 (m, 4H, H-piperazine) 2.42 (m, 4H, H-piperazine), 2.00 (t, J=7.2Hz, 2H,C3'-H), 0.94 (m, 2H, C2'-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 using tetramethylsilane as an internal standard.

IR spectra were recorded on a Specord 75 IR spectrophotometer in KBr pellets.

The IR spectra of the compounds showed the absorption bands at 1698--1782 cm^{-1} indicating the presence of five-membered CO-NH-CO system.

1-CHLOROMETHYL-DIBENZO[e.h]BICYCLO[2.2.2]OCTANE-2.3-DICARBOXIMIDE [I]

A mixture of 9-chloromethylanthracene (10.0 g, 44.11 mmol) and maleimide (4.0 g, 42.1 mmol) in o-dichlorobenzene (20 ml) was refluxed for 1 h. The product **I** was filtered off and crystallized from ethyl acetate.

N-(4-CHLOROBUTYL)-1-CHLOROMETHYL-DIBENZO[e.h]BICYCLO[2.2.2]OCTANE-2.3-DICARBOXIMIDE [II]

A mixture of imide **I** (2.7 g, 8.47 mmol) and 1-bromo-4-chlorobutane (2.7 g, 15.8 mmol) in acetonitrile (160 ml) was refluxed in the presence of anhydrous K_2CO_3 (3.0 g, 22 mmol) for 51 h. The inorganic precipitate was filtered off, the solvent was evaporated. Compound **II** was crystallized from octane.

N-(3-BROMOPROPYL)-1-CHLOROMETHYL-DIBENZO[e.h]BICYCLO [2.2.2]OCTANE-2.3-DICARBOXIMIDE [III]

A mixture of imide **I** (6.17 g, 19.06 mmol) and 1,3-dibromopropane (15.40 g, 76.27 mmol) in acetonitrile (150 ml) was refluxed in the presence of anhydrous K_2CO_3 (4.0 g, 29.3 mmol) for 50 h. The inorganic precipitate was filtered off, the solvent was evaporated. Compound **III** was crystallized from octane.

GENERAL PROCEDURE OF PREPARING N-[4-(4-ARYL-1-PIPERAZYNYL)BUTYL]-1-CHLOROMETHYL-DIBENZO [E.H]BICYCLO[2.2.2]OCTANE-2.3- DICARBOXIMIDE [IV-IX]

A mixture of the compound **II** (0.5 g, 1.09 mmol), anhydrous K_2CO_3 (0.5 g, 3.5 mmol), KI (0.2 g, 1.0 mmol) and the corresponding *N*-substituted piperazine (0.18-0.26 g, 1.10-1.22 mmol), was being refluxed in acetonitrile (50 ml) for 60 h. When the reaction was complete, the mixture was filtered and the solvent was evaporated. The residue was crystallized from an appropriate solvent.

GENERAL PROCEDURE OF PREPARING N-[3-(4-ARYL-1-PIPERAZYNYL)PROPYL]-1-CHLOROMETHYL-DIBENZO [e.h]BICYCLO[2.2.2]OCTANE-2.3- DICARBOXIMIDE [X-XV]

A mixture of the compound **III** (0.85 g, 1.89 mmol), anhydrous K_2CO_3 (0.9 g, 6.48 mmol),

KI (0.3 g, 1.8 mmol) and the corresponding *N*-substituted piperazine (0.61-0.73 g, 3.78 mmol), was refluxed in acetonitrile (50 ml) for 60 h. When the reaction was completed, the mixture was filtered and the solvent was evaporated. The residue was crystallized from appropriate solvent, mainly from octane.

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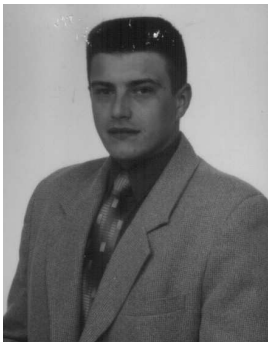
CURRICULUM VITAE



Mirosław Perliński was born in Warsaw in 1975. In 1994 he was graduated from secondary school in Warsaw. In 1995 he began studies in The Department of Pharmacy at The Medical University of Warsaw. In the 2000 he obtained the degree of Master of Pharmacy. Since 2000 he 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. In 2002 he obtained a Ph.D. in Pharmacology Science. During the time he was a co-author of 5 publications and 12 posters.