Acta Poloniae Pharmaceutica – Drug Research, Vol. 60 No. 3 pp. 183–189, 2003

ISSN 0001-6837
Polish Pharmaceutical Society

SYNTHESIS OF NEW N–SUBSTITUTED CYCLIC IMIDES WITH POTENTIAL ANXIOLYTIC ACTIVITY. XXV. DERIVATIVES OF HALOGENODIBENZO[e.h]BICYCLO[2.2.2]OCTANE–2.3–DICARBOXIMIDE

JERZY KOSSAKOWSKI and MIROSŁAW PERLIŃSKI

Chair and Department of Medical Chemistry, The Medical University of Warsaw, 3 Oczki Str., 02–007 Warsaw, Poland

Abstract: The preparation of a number of derivatives of dibenzo[e.h]bicyclo[2.2.2]octane –2,3–dicarboximide with an expected anxiolytic activity.

Keywords: halogenodibenzo[e.h]bicyclo[2.2.2]octane–2,3–dicarboximide, anxiolytic activity

Anxiolytic drugs without side effects are still being sought. During the last few years it has been reported that propranolol (Figure 1) and other β–adrenolytics produce activation of the central serotonin system (1,2) and have anxiolytic or antidepressive activity (3,4).

Also maprotiline and benzoctamine (Figure 2) 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 3–amine–2–hydroxypropyl group to achieve better activity.

The 3–amine–2–hydroxypropyl group is a part of the molecule of propranolol and it is considered to be responsible for pharmacological activity.

Previously we described the synthesis of cyclic imides and their derivatives (6,7,8).

As a result of our studies, we decided to present the synthesis of *N*–substituted derivatives of halogenodibenzo[e.h]bicyclo[2.2.2]octane–2,3–dicarboximide (Figure 3).

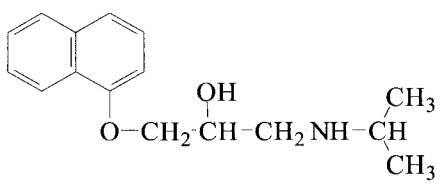


Figure 1. Propranolol.

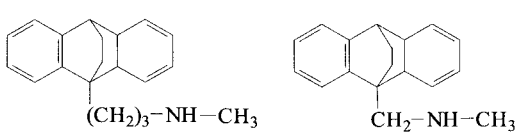


Figure 2. Maprotiline and Benzoctamine.

Imides **I (a, b, c, d,)** (Scheme 1), obtained in the Diels–Alder reaction of halogenoanthracenes and maleimide, were used as initial compounds. They were refluxed with 1–chloro–2,3–epoxypropane in the presence of anhydrous K_2CO_3 to give *N*–(2,3–epoxypropyl)–substituted imides **II (a, b, c, d)**, which were condensed with appropriate amines. The structures of the new derivatives of imides **II (a, b, c, d)** were confirmed by elemental analysis, IR and ^{1}H NMR spectra (Table 1).

Because of the fact that the compounds **III** (Figure 4) and **XVI** (Figure 5) have theoretically the best anxiolytic and antidepressive activity from the group of our substances, we have created space models using the Hyper Chem 5.02 software, according to the semiempiric method AM1 for better knowledge of their structures.

EXPERIMENTAL

Pharmacology

The hydrochlorides of the compounds **III** and **XVI** were tested for CNS activity at the Institute of

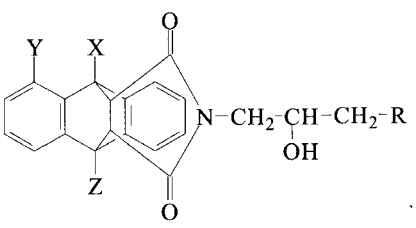
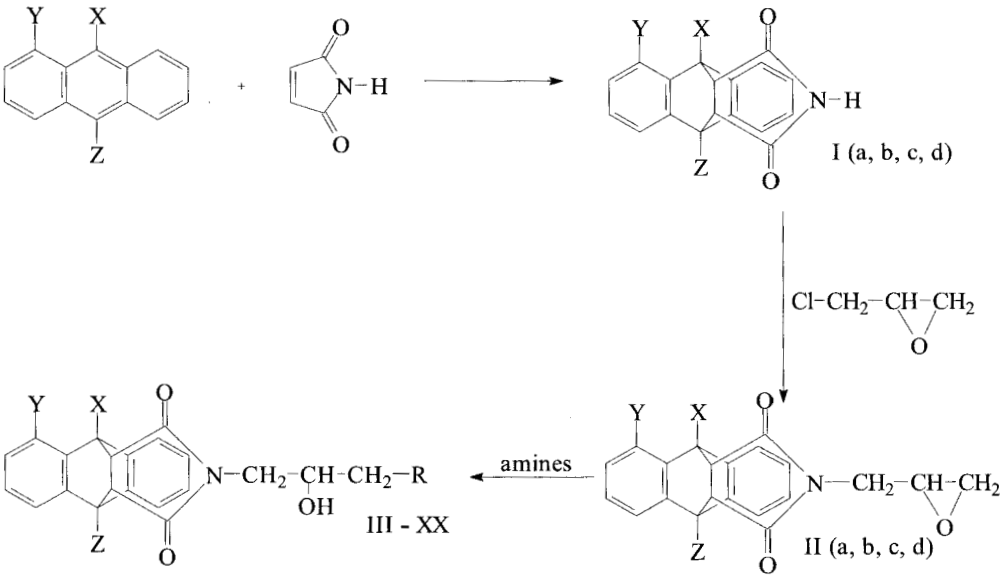


Figure 3. Derivatives of halogenodibenzo[e.h]bicyclo[2.2.2.]octane–2,3–dicarboximide.



amines = $-HN-CH(CH_3)_2$ $-HN-C(CH_3)_3$ $-N(CH_3)_2$ $-N(C_2H_5)_2$ $-N\langle\rangle N-CH_3$

III, VII, XII, XVI, **IV, VIII, XIII, XVII,** **V, IX, XIV, XVIII,** **VI, X, XV, XIX,** **XI, XX.**

	a	b	c	d
X	Cl	Cl	H	Br
Y	H	H	Cl	H
Z	H	Cl	H	H

Scheme 1. Scheme of the reactions.

Psychiatry and Neurology in Warsaw (headed by Professor dr hab. W. Kostowski). Adult male rats weighting 220–240 g were used. They were brought into the laboratory one week before the experiments and were housed with free access to food and water. In the Porsolt's test, the compounds were not effective in the used doses (1 and 5 mg/kg). They caused a rather low increase in locomotor activity. Unfortunately, these derivatives have not shown any anxiolytic activity in the open field test.

Chemistry

Melting points were determined in a capillary in an Electrothermal 9100 apparatus and were 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.

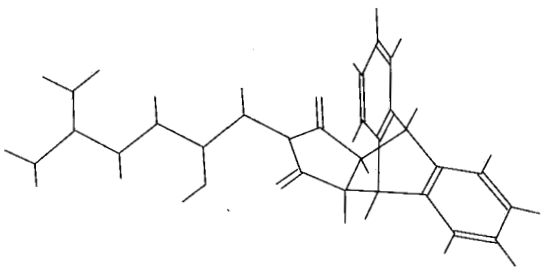


Figure 4. Space model of compound **III**.

Table1. Physical, analytical, IR and ^{1}H NMR spectral data of compounds [**I–XX**]

Comp. no	Formula Molecular weight	Solvent m.p [°C]	Yield %	Analysis Calculated/Found %C	%H	%N	^{1}H NMR (200 mHz, $CDCl_3$)
Ia	$C_{18}H_{12}NO_2Cl$ 309.75	ethyl acetate 291–292	91	69.78 69.90	3.90 4.20	4.52 4.51	10.98 (br. s 1H, CONH), 7.71 (m, 1H, H_{arom}), 7.56 (m, 2H, H_{arom}), 7.31 (m, 5H, H_{arom}), 4.85 (s, 1H, H_a), 3.40 (d, J=1.4 Hz, 2H, H_b, H_c).
Ib	$C_{18}H_{11}NO_2Cl_2$ 344.28	benzene 293–294	92	62.78 62.75	3.20 3.35	4.06 4.06	11.15 (s, 1H, NH), 7.80 (dd, J_1=5.6Hz, J_2=3.0Hz, 2H, H_{arom}), 7.66 (dd, J1=5.6Hz, J2=3.2Hz, 2H, H_{arom}), 7.43 (m, 4H, H_{arom}), 3.59 (s, 2H, H_b, H_c)
Ic	$C_{18}H_{12}NO_2Cl$ 309.75	ethyl acetate 253–254	89	69,80 70.01	3.90 3.99	4.52 4.54	7.91 (br. S., 1H, NH), 7.48–7.01 (m, 7H, H_{arom}), 5.28 (m, 1H, C1–H), 4.76 (d, J=1.8 Hz, 1H, H_a), 3.22(m, 2H, H_b, H_c).
Id	$C_{18}H_{12}NO_2Br$ 354.19	benzene 277–278	85	61.03 60.96	3.42 3.46	3.95 3.92	7.89(m,, 1H, H_{arom}), 7.73(m, 1H, H_{arom}), 7.53(br.s, 1H, NH), 7.40–7.20(m, 6H, H_{arom}), 4.79(d, J=3.2Hz, 1H, H_c), 3.48(d, , J=8.8Hz, 1H, H_a), 3.35(dd, J=8.8Hz, 3.2Hz, 1H, H_b).
IIa	$C_{21}H_{16}NO_3Cl$ 365.85	methanol 195–196	79	68.94 68.74	4.41 4.70	3.83 3.84	7.83 (m, 1H, H_{arom}), 7.70 (m, 1H, H_{arom}), 7.43–7.20 (m, 6H, H_{arom}), 4.81 (d, J=1.6 Hz, 1H, H_a), 3.51 (m, 1H, C1'–H), 3.40 (m, 1H, C1'–H) 3.36 (d, J=1.8 Hz, 2H, C2–H, C3–H), 2.36–2.06(m, 3H, C2'–H, C3'–H).
IIb	$C_{21}H_{15}NO_3Cl_2$ 400.26	methanol 245–246	61	63.02 62.45	3.78 3.75	3.50 3.41	7.87 (dd, J_1=5.6 Hz, J_2=3.2Hz, 2H, H_{arom}), 7.73 (m, 2H, H_{arom}), 7.36 (m, 4H, H_{arom}), 3.52 (m, 1H, C2'–H), 3.48 (m, 2H, H_b, H_c), 3.12 (2d, J_1=5.6Hz, J_2=6.0Hz, 1H,C1'–H), 2.32 (m, 2H, C1'–H, C3'–H), 2.07 (m, 1H,C3'–H).
IIc	$C_{21}H_{16}NO_3Cl$ 365.82	methanol 176–177	42	68.95 68.77	4.41 4.34	3.83 3.87	7.46–7.04 (m, 7H, H_{arom}), 5.37 (m, 1H, C1–H), 5.30 (m, 1H, C1–H), 4.80 (d, J=2.6Hz,1H, C4–H), 3.49 (m, 1H, C2'–H), 3.23 (m, 2H, H_b, H_c), 3.05 (m, 1H, C1',C3'–H), 2.33 (m, 1H, C1',C3'–H), 2.22 (m, 1H, C1',C3'–H), 2.14 (m, 1H, C1',C3'–H).

Table 1. (continued)

Comp. no	Formula Molecular weight	Solvent m.p [°C]	Yield %	Analysis Calculated/Found %C	%H	%N	^{1}H NMR (200 mHz, $CDCl_3$)
IId	$C_{21}H_{16}NO_3Br$ 475.20	benzene 185–186	64	61.47 61.27	3.93 3.90	3.41 3.32	7.90 (m, 1H, H_{arom}), 7.72 (m, 1H, H_{arom}), 7.40–7.20 (m, 6H, H_{arom}), 4.83 (dd, J_1= J_2=3.4Hz,1H, H_a), 3.53 (m, 1H, C1'–H), 3.47 (m, 1H, H_b), 3.34 (m, 1H, H_c), 3.08 (m, 1H, C1'–H), 2.36–2.06(m,3H,C2',C3'–H).
III	$C_{24}H_{25}N_2O_3Cl$ *0.5 H_2O*HCl 470.50	octane 231–232	74	61.26 61.09	5.78 5.80	5.95 5.97	9.28 (br.s., 1H, NH^+), 7.79–7.02 (m, 8H, H_{arom}), 4.72 (s, 1H, H_a) 4.10 (br.s., 1H, OH) 3.03–2.61 (m, 6H, C1'–C4'–H), 1.42 (s, 6H, 2*CH_3)
IV	$C_{25}H_{27}N_2O_3Cl$ *0.5H_2O 447.97	hexane 69–70	62	67.03 66.95	6,30 6,40	6,25 6.08	7.82 (m, 1H, H_{arom}), 7.69 (m, 1H, H_{arom}), 7.42–7.21 (m, 6H, H_{arom}), 4.81 (s,1H, H_a), 3.36 (dd, J_1=J_2=1.4Hz, 2H, H_b, H_c), 3.19–3.01 (m, 2H, OH, NH), 2.17 (t of d, J_1=9.1 Hz, J_2=3.6 Hz, 1H, C1'–H), 1.88 (m, 4H, C3'–H), 1.05, 1.04 (s ,9H, $(CH_3)_3$),
V	$C_{23}H_{23}N_2O_3Cl$ *0.5 H_2O 419.92	octane 67–68	81	66.50 66.24	5.70 5.60	6.74 6.62	7.82 (m., 1H, H_{arom}) 7.70 (m, 1H, H_{arom}) 7.43–7.22 (m, 6H, H_{arom}), 4.82 (s, 1H, H_a) 3.36 (d, J=1.2 Hz, 2H, H_b, H_c) 3.32–3.14 (m, 2H,OH,C2'–H), 2.15 (s, 6H, $N(CH_3)_2$) 2.08–1.68 (m, 4H, C1'–H, C3'–H)
VI	$C_{25}H_{27}N_2O_3Cl$ 438.96	methanol 180–181	53	68.41 67.88	6.20 6.15	6.38 6.49	7.81 (m, 1H, H_{arom}), 7.69 (m, 1H, H_{arom}), 7.42–7.18 (m, 6H, H_{arom}), 4.81 (s,1H, H_a), 3.49 (d, J=0.6 Hz, 2H, H_b, H_c), 3.18 (m, 4H, OH, C2'–H, C1'–H), 2.42 (m, 4H, N–CH_2), 2.12–1.84 (m, 2H, N–CH_2), 0.95 (t ,6H, J=7.2 Hz, 2*CH_3),
VII	$C_{24}H_{24}N_3O_2Cl_2$ 459,38	octane 155–156	84	62.75 62.35	5.27 5.30	6.10 6.04	7.86 (dd, J_1=5.6 Hz, J_2=3.2Hz, 2H, H_{arom}), 7.73 (m, 2H, H_{arom}), 7.36 (m, 4H, H_{arom}), 3.48 (s, 2H, H_b, H_c), 3.32 (m, 1H,C2'–H), 3.24–3.16 (m, 2H, C1'–H), 2.66 (m, 1H,C1''–H), 2.15 (m, 1H, C3'–H), 1.94 (m, 3H,C3'–H, NH, OH) 1,03 (d, J=6.2Hz, 6H, C2''–H).

Table 1. (continued)

Comp. no	Formula Molecular weight	Solvent m.p [°C]	Yield %	Analysis Calculated/Found %C	%H	%N	^{1}H NMR (200 mHz, $CDCl_3$)
VIII	$C_{25}H_{26}N_2O_3Cl_2$ *0.25 H_2O 477.90	methanol 169–170	64	62.83 62.75	5.59 5.49	5.86 5.72	7.86 (dd, J_1=5.6 Hz, J_2=3.4Hz, 2H, H_{arom}), 7.72 (m, 2H, H_{arom}), 7.35 (m, 4H, H_{arom}), 3.48 (s, 2H, H_b, H_c), 3.32 (m, 1H,C2'–H), 3.20–3.02 (m, 2H, C1'–H), 2.14 (dd, J_1=12.2Hz, J_2=4.0Hz, 1H, C3'–H), 2.03 (br.s, 2H, NH, OH), 1.83 (dd, J_1=12.4Hz, J_2=5.2Hz, 1H,C3'–H), 1.04 (s ,9H, C–$(CH_3)_3$).
IX	$C_{23}H_{22}N_2O_3Cl_2$ 445.351	octane 207–208	50	62.03 62.14	4.98 5.07	6.29 6.34	7.86 (dd, J_1=5.6 Hz, J_2=3.2Hz, 2H, H_{arom}), 7.73 (dd, J_1=5.6Hz, J_2=3.2Hz, 2H, H_{arom}), 7.35 (m, 4H, H_{arom}), 3.48 (s, 2H, H_b, H_c), 3.25 (m, 3H, C1'–H,C2'–H), 2.66 (br.s, 1H, OH), 2.14 (s, 6H, N–$(CH_3)_2$), 1.99 (m, 1H, C3'–H), 1.69 (dd, J_1=12.4Hz, J_2=2.6Hz, 1H,C3'–H).
X	$C_{25}H_{26}N_2O_3Cl_2$ 473.40	methanol 157–158	74	63.43 63.44	5.54 5.43	5.92 5.92	7.86 (dd, J_1=5.6 Hz, J_2=3.0Hz, 2H, H_{arom}), 7.73 (m, 2H, H_{arom}), 7.35 (m, 4H, H_{arom}), 3.48 (s, 2H, H_b, H_c), 3.39–3.11 (m, 3H, C1'–H,C2'–H), 2.41 (m, 4H, N–$(CH_2)_2$), 2.04 (dd, J_1'=13Hz, J_2=8.8Hz, 1H, C3'–H), 1.88 (dd, J_1=12Hz, J_2=8.0Hz, 1H, C3'–H), 0.95 (t, J=7.2Hz, 6H,C$(CH_3)_2$).
XI	$C_{26}H_{27}N_3O_3Cl_2$ *0.33 H_2O 506.43	methanol 77–78	68	61.66 61.64	5.50 5.54	8.30 8.16	7.86 (dd, J_1=5.6 Hz, J_2=3.4Hz, 2H, H_{arom}), 7.36 (m, 4H, H_{arom}), 7.32 (m, 2H, H_{arom}), 3.48 (s, 2H, H_b, H_c), 3.29 (m, 3H, C1'–H,C2'–H), 2.40 (m, 8H, H–piperazine), 2.27 (s, 3H, N–CH_3), 1.99 (m, 1H, C3'–H), 1.76 (m, 1H,C3'–H).
XII	$C_{24}H_{25}N_2O_3Cl$ 424.93	methanol 121–122	58	67.84 68.24	5.93 5.69	6.59 6.18	7.46–6.96 (m, 7H, H_{arom}), 5.24 (m, 1H, C1–H), 5.30 (d, J=2.0Hz, 1H, C1–H), 4.73 (m, 1H, C4–H), 3.91 (m, 1H, C2'–H), 3.43–2.92 (m, 5H, C1',C3'–H, H_b, H_c), 2.70 (m, 1H, C3'–H), 2.48 (g, 1H, C4'–H), 1.32 (m, 6H, 2*CH_3).
XIII	$C_{25}H_{27}N_2O_3Cl$ *HCl*H_2O 493.43	methanol/ ether 179–180	50	60.85 60.90	6.13 6.10	5.68 5.68	9.46 (br.s., 1H, NH), 7.49 (br.s., 1H, NH), 7.23–6.98 (m, 7H, H_{arom}), 5.29 (m, 1H, OH), 5.18 (d, J=3.0Hz,1H, C1–H), 4.71 (m, 1H, C4–H), 4.11 (br.s., 1H, C2'–H), 3.34 (m, 2H, H_b, H_c), 3.13 (m, 1H, C3'–H), 2.88 (m, 2H, C1'–H), 2.60 (m, 1H, C3'–H), 1.43 (s, 9H, 3*–CH_3).

Table 1. (continued)

Comp. no	Formula Molecular weight	Solvent m.p [°C]	Yield %	Analysis Calculated/Found %C	%H	%N	^{1}H NMR 200 mHz, $CDCl_3$
XIV	$C_{23}H_{23}N_2O_3Cl$ 411.56	octane 165–166	67	67.12 67.04	5.63 5.57	6.81 6.79	7.45–7.01 (m, 7H, H_{arom}), 5.33 (m, 1H, C1–H), 4.81 (m, 1H, C4–H), 3.39–3.08 (m, 5H, C1'–H, C2'–H, H_b, H_c), 2.85 (s, 1H, OH), 2.15 (s, 3H, N–CH_3), 2.14 (s, 3H, N–CH_3), 2.00 (m, 1H, C3'–H), 1.77 (m, 1H, C3'–H).
XV	$C_{25}H_{27}N_2O_3Cl$ * HCl 475.42	methanol/ ether 259–260	64	63.16 62.95	5.94 6.09	5.89 5.98	11.20 (m, 1H, NH), 7.45–7.06 (m, 7H, H_{arom}), 5.30 (m, 1H, C1–H), 4.80 (s, 2H, C2–H, C3–H), 4.05 (m, 1H, C2'–H), 3.32 (m, 4H, C1'–H, C3'–H), 3.14 (m, 4H, $N(CH_2)_2$), 2.70 (m, 2H, C4–H, OH), 1.37 (m, 6H, 2*CH_3).
XVI	$C_{24}H_{25}N_2O_3Br$ *0.75 H_2O 482.90	octane 59–60	86	59.69 59.61	5.53 5.41	5.80 5.70	7.89 (m, 1H, H_{arom}), 7.71 (m, 1H, H_{arom}), 7.40–7.20 (m, 6H, H_{arom}), 4.81(d, J=3.2Hz, 1H, H_a), 3.50(dd, J_1=8.8Hz, J_2=1.6Hz, 1H, H_b), 3.40–3.11(m, 2H, H_c, NH), 2.75 (m, 1H, C2'–H), 2.25 (m, 5H, C1'–H,C3'–H, OH), 2.06 (m, 1H, CH), 1.09 (d, J=2.0Hz, 3H, CH_3), 1.06 (d, J=2.0Hz, 3H, CH_3).
XVII	$C_{25}H_{27}N_2O_3Br$ *HCl*0.25 H_2O 524.37	$HCl_{methanol}$, methanol/ ether 291–292	62	57.26 57.25	5.48 5.30	5.34 5.33	8.72 (m, 1H, NH), 8.30 (m, 1H, NH), 7.78 (m,, 1H, H_{arom}), 7.55 (m, 1H, H_{arom}), 7.28 (m, 6H, H_{arom}), 5.55 (m, 1H, OH), 4.90 (d, J=3.2Hz, 1H, H_b), 3.58 (d, J=8.4Hz, 1H, H_a), 3.48 (dd, J=8.6Hz, 3.0Hz, 1H, H_c), 3.13–2.72 (m, 3H, C1',C2'–H), 2.20–2.05 (m, 2H, C3'–H), 1.23 (s, 9H, N–$(CH_3)_3$).
XVIII	$C_{23}H_{23}N_2O_3Br$ *0.25 H_2O 459.86	octane 142–143	65	60.07 60.05	5.15 5.04	6.09 5.99	7.89 (m, 1H, H_{arom}), 7.73(m, 1H, H_{arom}), 7.40–7.19 (m, 6H, H_{arom}), 4.82 (d, J=3.0Hz, 1H, H_c), 3.46 (2d, J=1.4Hz, 1H, H_b), 3.37–3.12 (m, 4H, H_c, C1'–H, C2'–H), 2.55 (br.s, 1H, OH), 2.144(s, 3H, CH_3), 2.140 (s, 3H, CH_3), 2.01 (m, 1H, C3'–H), 1.73 (m, 1H, C3'–H).

Table 1 (continued)

Comp. no	Formula Molecular weight	Solvent m.p [°C]	Yield %	Analysis Calculated/Found %C	%H	%N	^{1}H NMR (200 mHz, $CDCl_3$)
XIX	$C_{25}H_{27}N_2O_3Br$ *0,25 H_2O 487,91	hexane 171–172	51	61.54 61.43	5.68 5.73	5.74 5.72	7.89 (m, 1H, H_{arom}), 7.72(m, 1H, H_{arom}) 7.40–7.17 (m, 6H, H_{arom}), 4.82 (d, J=3.0Hz, 1H, H_c), 3.53–3.06(m, 6H, C1',C2', H_b, H_c,OH), 2.56–2.28 (m,4H, N–CH_2), 2.15–1.88 (m, 2H, N–CH_2), 0.97 (t, J=7.2Hz, 6H, N–CH_2–CH_3).
XX	$C_{26}H_{28}N_3O_3Br$ *0,75 H_2O 523,95	hexane 66–67	71	59.60 59.86	5.67 5.37	8.02 8.02	7.89 (m, 1H, H_{arom}), 7.72 (m, 1H, H_{arom}), 7.40–7.20 (m, 6H, H_{arom}), 4.81 (d, J=3.2Hz, 1H, H_a), 3.46 (dd, J_1=1.4Hz, J_2=2.8Hz, 1H, H_c), 3.37–3.10 (m, 5H, C2'–H, H–piperazine, H_b), 2.39 (m, 7H, C1'–H, H–piperazine), 2.27(s, 4H, OH,N–CH_3), 2.01 (m, 1H, C3'–H), 1.81 (m, 1H, C3'–H).

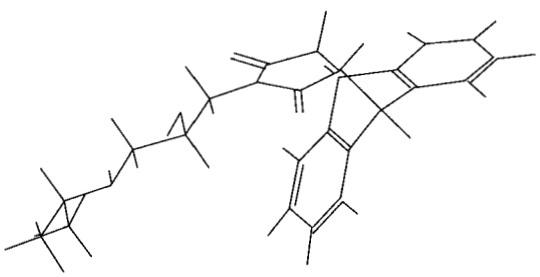


Figure 5. Space model of compound **XVI**.

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.

HALOGENODIBENZO[e.h]BICYCLO[2.2.2]OCTANE–2,3–DICARBOXIMIDE [**I (a, b, c, d)**].

A mixture of halogenoanthracene (~0.05 mol) and maleimide (~0.05 mol) in o–dichlorobenzene (20 ml) was refluxed for 1 h. The products **I (a, b, c, d)** were filtered off and crystallized from appropriate solvents (Table 1).

N–(2,3–EPOXYPROPYL)HALOGENODIBENZO[e.h]BICYCLO[2.2.2]OCTANE–2,3–DICARBOXIMIDE [**II (a, b, c, d)**].

A mixture of imide **I (a, b, c, d)** (0.015 mol) and 1–chloro–2,3–epoxypropane (40 cm^3) was refluxed in the presence of anhydrous K_2CO_3 (4.5 g, 0.033 mol) for ~50 h. The inorganic precipitate was filtered off, the solvent was evaporated. Compounds **II (a, b, c, d)** were crystallized from the appropriate solvents (Table 1).

GENERAL PROCEDURE OF PREPARING N–[(3–AMINE–2–HYDROXY)PROPYL]–HALOGENODIBENZO[e.h]BICYCLO[2.2.2]OCTANE–2,3–DICARBOXIMIDE [**III–XX**].

A mixture of the compound **II (a, b, c, d)** (~0.003 mol), and the corresponding amine (~0.015 mol), was being refluxed in a mixture of methanol and water (39 : 1 V/V) (40 cm^3) for 50 h. When the reaction was complete, the mixture was filtered and the solvent was evaporated. The residue was crystallized from appropriate solvents (Table 1).

RESULTS

In this study we have presented the synthesis of 26 new derivatives of dibenzo[e.h]bicyclo[2.2.2]

octane –2,3–dicarboximide for potential use in the treatment of anxiety. Compounds **III** and **XVI** were evaluated for anxiolytic activity. Unfortunately, the pharmacological investigation proved a rather low anxiolytic activity of the obtained compounds.

REFERENCES

1. Lasek R., Muller M.: Psychiatr. Neurol. Med. Psychol. 37(7), 385, (1985).
2. Suzman M.M.: Postgrad. Med. J. 52 (4), 168, (1976).
3. Riblet L., Taylor D.P., Eison M.S., Stanton H.C.: J. Clin. Psychiatr. 11, 43, (1982).
4. Wu. Y–H, Smith K.R., Raybourn J.W., Kissel J.W.: J. Med. Chem. 867,12, (1967).
5. Podlewski K.J., Chwalibogowska–Podlewska A.: Leki współczesnej terapii 2000.
6. Zawadowski T., Zadrożna A., Rump S., Jakowicz I.: Acta Polon. Pharm. 467, 51, (1994).
7. Kossakowski J., Sroka T.K.: Acta Polon. Pharm – Drug Res. 56, 85 (Suppl.), (1999).
8. Kossakowski J., Sroka T.K.: Acta Polon. Pharm – Drug Res. 56, 89 (Suppl.), (1999).
9. Kossakowski J., Kuśmierczyk J.: Pharmazie 1, 55, (2000).
10. Kossakowski J., Zawadowski T., Turło J., Kleps J.: IL Farmaco 53, 169, (1998).
11. Porsolt R.D., Anton G., Blavet N., Jalfre M.: Eur. J. Pharmacol. 47, 379, (1978).

Received: 30.07.02