A mixture of imide **I** (6 g, 19.78 mmole), and 1–chloro–2.3–epoxypropane (90 ml) was refluxed in the presence of anhydrous K_2CO_3 (4.5 g, 32.60 mmol) for 14 h. The inorganic precipitate was filtered off, the excess of 1–chloro–2,3–epoxypropane was evaporated. Compound **IV** was crystallized from hexane.

A GENERAL PROCEDURE FOR PREPARATION OF N–[4–(4–ARYL–1–PIPERAZINYL)–BUTYL]–1–ACETYLDIBENZO–[e.h]–BICYCLO[2.2.2]–OCTANE–2,3–DICARBOXIMIDE [**V–X**]

A mixture of compound **II** (1.2–1 g, 2.94–2.45 mmole), anhydrous K_2CO_3 (1.2–1 g, 8.69–7.24 mmole), KI (0.2 g, 1.0 mmole) and the corresponding N–substituted piperazine (0.97–0.44 g, 5.95–2.44 mmole) was refluxed in acetonitrile (30–50 ml) for 50 h. When the reaction was completed as found by TLC (silica gel, developing system – chloroform:methanol) the mixture was filtered off and the solvent was evaporated. The residue was crystallized from an appropriate solvent.

A GENERAL PROCEDURE FOR PREPARATION OF N–[3–(4–ARYL–1–PIPERAZINYL)PROPYL]–1–ACETYLDIBENZO–[e.h]–BICYCLO[2.2.2]–OCTANE–2,3–DICARBOXIMIDE [**XI–XV**]

A mixture of compound **III** (0.9 g, 2.05 mmole), anhydrous K_2CO_3 (0.9 g, 6.52 mmole), KI (0.2 g, 1.0 mmole) and the corresponding N–substituted piperazine (0.37–0.72 g, 2.05–4.09 mmole) was refluxed in acetonitrile (50 ml) for 50 h. When the reaction was completed according to TLC (silica gel, developing system – chloroform:methanol), the mixture was filtered and the solvent was evaporated. The residue was crystallized from an appropriate solvent.

A GENERAL PROCEDURE FOR PREPARATION OF N–(–3–AMINE–2–HYDROXYPROP–1–YL)– 1–ACETYLDIBENZO–[e.h]–BICYCLO[2.2.2]–OCTANE–2,3–DICARBOXIMIDE [**XVI–XXI**]

A mixture of compound **IV** (0.5 g, 1.33 mmole), and the corresponding amine (1.5 cm^3) was refluxed in a methanol solution (25 ml) for 4 h. When the reaction was completed the solvent was evaporated. The residue was crystallized from hexane or octane.

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SYNTHESIS OF NEW *N*–SUBSTITUTED CYCLIC IMIDES WITH POTENTIAL ANXIOLYTIC ACTIVITY. XXIII. DERIVATIVES OF 2'–CHLORODIBENZO[e.h]BICYCLO[2.2.2]OCTANE–2,3–DICARBOXIMIDE

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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 is described.

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

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 the 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) (Figure 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–piperazineal-

kyl group to achieve better activity. The 4–aryl(hetero-aryl)–1–piperazinealkyl group is a part of the buspirone molecule and is considered to be responsible for pharmacological activity.

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

In this communication we report on the syntheses of *N*–substituted derivatives of 2'–chlorodibenzo[e.h]-bicyclo[2.2.2]octane–2,3–dicarboximide (Figure 2).

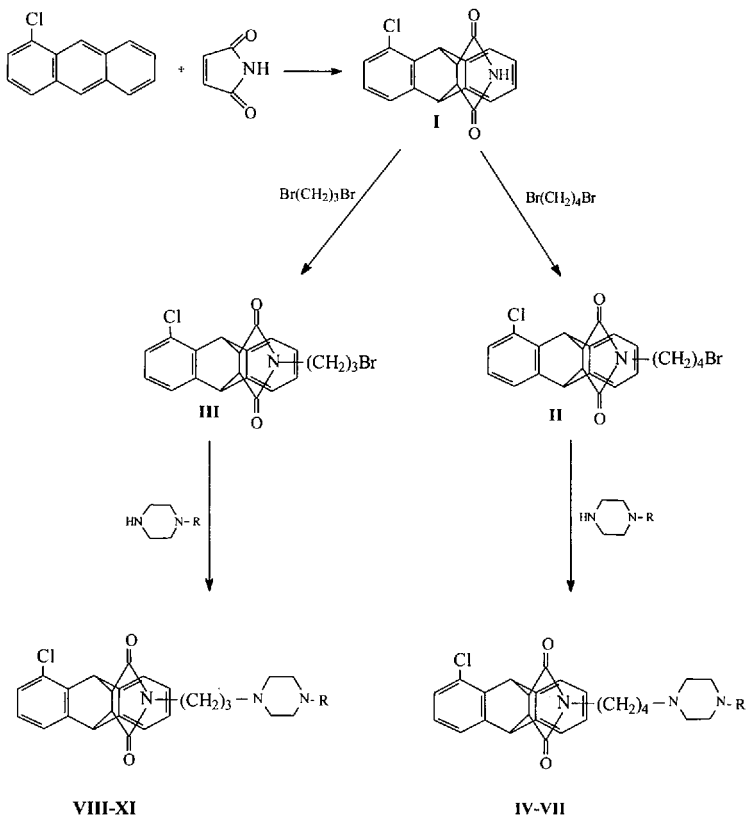
Imide **I** (Scheme 1), obtained in Diels–Alder reaction of 1–chloroanthracene and maleimide, was used as a starting compound. It was refluxed with 1,3–dibromopropane or 1,4–dibromobutane in acetonitrile in the presence of anhydrous K_2CO_3 to give *N*–(3–bromopropyl)– **III** or N–(4–bromobutyl)–substituted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

Because compounds **IV** and **V** (Figure 3) 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 semiempirical method AM1 for a better knowledge of their structure.

EXPERIMENTAL

Melting points were determined in a capillary tubes in an 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 are expressed in ppm using tetramethylsilane as an internal standard.

Figure 1. Maprotiline and benzoctamine



Scheme 1. Scheme of the reactions

2'–CHLOROBENZOBENZ[e.h]BICYCLO[2.2.2]OCTANE–2,3–DICARBOXIMIDE [**I**].

A mixture of 1–chloroanthracene (10.0 g, 0.047 mole) and maleimide (4.6 g, 0.047 mole) in o–dichlorobenzene (20 ml) was refluxed for 1 h. Product **I** was filtered off and crystallized from ethyl acetate.

N–(4–BROMOBUTYL)–2'–CHLORODIBENZO[e.h] BICYCLO[2.2.2]OCTANE–2,3–DICARBOXIMIDE [**II**].

A mixture of imide **I** (3.0 g, 0.01 mole) and 1,4–dibromobutane (4.3 g, 0,02 mole) in acetonitrile (160 ml) was refluxed in the presence of anhydrous K_2CO_3 (3.0 g, 0.02 mole) for 51 h. The inorganic precipitate was filtered off, the solvent was evaporated. Compound **II** was crystallized from octane.

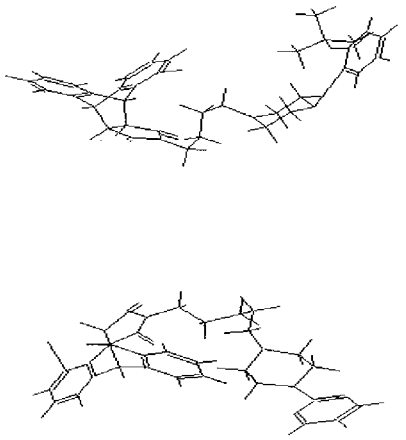


Figure 3. Space models of compounds **IV** and **V**

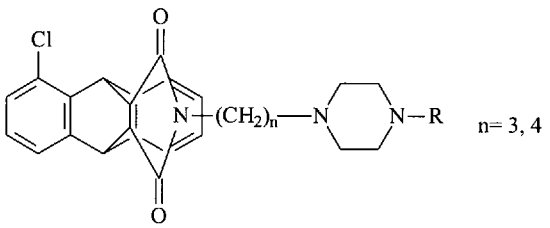


Figure 2. Derivatives of 2'–chlorobenzobenz[e.h.]bicyclo[2.2.2.]octane–2,3–dicarboximide

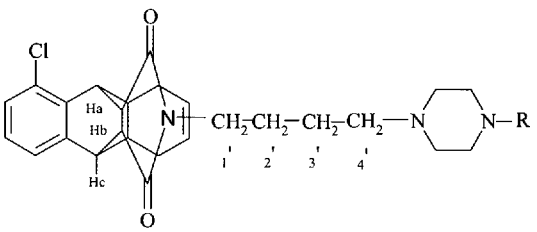


Figure 4. Scheme of our compounds with explanation

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

Comp. No.	Formula Molecular weight	Solvent mp [°C]	Yield %	Analysis Calculated/Found %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
I	$C_{18}H_{12}NO_2Cl$ 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).
II	$C_{22}H_{19}NO_2BrCl$ 444.81	octane 195–196	42	59.40 60.05	4.30 4.41	3.15 3.46	7.36–7.02 (m, 7H, H_{arom}), 5.30 (d, J=2 Hz, 1H, C1–H), 4.80, (d, J=2Hz, 1H, H_c), 3.16 (m, 4H, C1',C4',H_a, H_b), 1.22 (m, 2H, C2'–H), 1.00 (m, 2H, C3'–H)
III	$C_{21}H_{17}NO_2BrCl$ 430.73	octane 180–181	73	58.56 58.65	3.98 4.01	3.25 3.23	7.46–7.06 (m, 7H, H_{arom}), 5.36 (d, J=2.6 Hz, 1H, C1–H), 5.30 (d, J=2.0 Hz, 1H, C1–H), 4.80 (m, 1H, H_c), 3.26 (m, 2H, C1'–H), 3.19 (t, J=1.4 Hz, 2H, H_a, H_b), 2.85–2.69 (m, 2H, C3'–H), 1.50–1.34 (m, 2H, C2'–H).
IV	$C_{33}H_{33}N_3O_3Cl$ *0.5 H_2O 565.12	hexane 54–55 column. chrom. chl:met. 98:2	63	70.14 70.43	6.24 6.24	7.43 7.28	7.46–6.85 (m, 11H, H_{arom}), 5.30 (m, 1H, C1–H), 4.80 (s, 1H, H_c), 3.87 (s, 3H, OCH_3), 3.22–3.07 (m, 8H, C1'–H, H_a, H_b, $(CH_2)_2$–Nφ), 2.71 (m, 4H, N–$(CH_2)_2$,), 2.32 (m, 2H, C4'–H), 1.21 (m, 2H, C2'–H), 0.86 (m, 2H, C3'–H)

Table 1. (continued)

Comp. No.	Formula Molecular weight	Solvent mp [°C]	Yield %	Analysis Calculated/Found %C	%H	%N	^{1}H NMR, (200MHz, $CDCl_3$)
V	$C_{30}H_{30}N_5O_2Cl$ 528.07	hexane 141–142	67	68.23 68.35	5.73 5.91	13.26 13.17	8.30 (d, J=4.6 Hz, 2H, $H_{\alpha pyr}$), 7.46–7.01 (m, 7H, H_{arom}), 6.47 (dd, J_1=J_2=4.8 Hz, 2H, $H_{\beta pyr}$), 5.36 (d, J=2.6 Hz, 1H, C1–H), 5.29 (d, J=2.2 Hz ,1H, C1–H), 4.80 (d, J= 2.4Hz, 1H, H_c), 3.81 (t, J=5 Hz, 4H, $(CH_2)_2$–Nφ,), 3.17 (m, 4H, C1'–H, H_b, H_c), 2.42 (m, 4H, N–$(CH_2)_2$,), 2.18 (m ,2H, C4'–H), 1.15 (m, 2H, C2'–H), 0.82 (m, 2H, C3'–H).
VI	$C_{32}H_{31}N_3O_2ClF$ *0.75 H_2O 557.59	octane 149–150 column. chrom. chl:met. 99:1	53	68.93 68.83	5.87 5.68	7.54 7.53	7.46–6.83 (m, 11H, H_{arom}), 5.36 (d, J= 2.8Hz, 1H, C1–H), 5.29 (d, J=2.2 Hz, 1H, C1–H), 4.80 (d, J= 2.6Hz, 1H, H_c), 3.22–3.07 (m, 8H, C1'–H, H_a, H_b, $(CH_2)_2$–Nφ), 2.52 (m, 4H, N–$(CH_2)_2$), 2.19 (m, 2H, C4'–H), 1.13 (m, 2H, C2'–H), 0.85 (m, 2H, C3'–H)
VII	$C_{31}H_{31}N_4O_2Cl$ 581.13	octane 146–147	60	70,64 70,33	5,93 6,17	10,63 10,38	8.18 (m, 1H, $H_{\alpha pyr}$), 7.51–7.01 (m, 8H, H_{arom}), 6.62 (m, 2H, $H_{\alpha pyr}$), 5.36 (d, J=3 Hz, 1H, C1–H) 5.29 (d, J=2.2 Hz, 1H, C1–H) 4.80 (d, J=2.8 Hz, 1H, H_c), 3.52 (t, J=5Hz, 4H, $(CH_2)_2$–Nφ), 3.17 (m, 4H, C1'–H, H_a, H_b), 2.48 (t, J=5.0 Hz, 4H, N–$(CH_2)_2$), 2.18 (m, 2H, C4'–H), 1.13 (m, 2H, C2'–H), 0.83 (m, 2H, C3'–H).
VIII	$C_{32}H_{32}N_3O_3Cl$ *0.5 H_2O 551.10	octane 148–149	46	69.74 69.84	6.03 6.04	7.63 6.93	7.46–6.83 (m, 11H, H_{arom}), 5.36 (d, J=2.6Hz, 1H, C1–H), 5.30 (d, J=2.0Hz, 1H, C1–H), 4.80 (d, J=2.4Hz, 1H, C4–H), 3.85 (s, 3H, OCH_3), 3.37–3.12 (m, 8H, $(CH_2)_2$–Nφ, C1'–H, C2–H, C3–H), 3.06 (m, 4H, N$(CH_2)_2$), 2.10 (m, 2H, C3'–H), 1.01 (m, 2H, C2'–H).
IX	$C_{29}H_{28}N_5O_2Cl$ 514.04	methanol 156–157	48	67.76 67.70	5.49 5.50	13.63 13.48	8.30 (d, J=5.0 Hz, 2H, $H_{\alpha pyr}$), 7.45–6.90 (m, 7H, H_{arom}), 6.47 (dd, J_1= J_2=5Hz,1H, $H_{\beta pyr}$), 5.36 (d, J=2.6 Hz, 1H, C1–H), 5.30 (d, J=2.2 Hz, 1H, C1–H), 4.80 (d, J= 2.8Hz, 1H, C4–H), 3.78 (t, J=5Hz,4H, $(CH_2)_2$Nφ), 3.19 (m, 4H, C1'–H, H_b, H_c), 2.34 (m, 4H, N–$(CH_2)_2$), 2.03 (m ,2H, C3'–H), 1.00 (m, 2H, C2'–H).
X	$C_{31}H_{29}N_3O_2ClF$ *0.25 H_2O 534.55	octane 149–150	47	69.65 69.68	5.56 5.50	7.86 6.89	7.46–6.82 (m, 11H, H_{arom}), 5.36 (d, J=2.6Hz, 1H, C1–H), 5.30 (d, J=2.0Hz, 1H, C1–H), 4.80 (m, 1H, C4–H), 3.37–2.79 (m, 8H, $(CH_2)_2$–Nφ, C1'–H, H_b, H_c), 2.47 (m, 4H, N$(CH_2)_2$), 2.07 (m, 2H, C3'–H), 1.02 (m, 2H, C2'–H).
XI	$C_{30}H_{29}N_4O_2Cl$ 513.05	octane 171–172	63	70.23 70.24	5.70 5.71	10.92 10.84	8.18 (m, 1H, $H_{\alpha pyr}$), 7.50–7.03 (m, 8H, H_{arom}), 6.61 (m, 2H, $H_{\beta pyr}$), 5.36 (d, J=2.6 Hz, 1H, C1–H), 5.29 (d, J=2.0 Hz, 1H, C1–H) 4.80 (d, J=2.6 Hz, 1H, C4–H), 3.50 (t, J=5Hz, 4H, $(CH_2)_2$Nφ), 3.50 (t, J=5Hz,4H,$(CH_2)_2$Nφ), 3.19 (m, 4H, C1'–H, H_c, H_b), 2.40 (m, 4H, N–$(CH_2)_2$, 2.40 (m, 2H, C3'–H) 1.01 (m, 2H, C2'–H).

N–(3–BROMOPROPYL)–2'–CHLORODIBENZO-[e.h]BICYCLO[2.2.2]OCTANE–2,3–DICARBOXIMIDE [**III**].

A mixture of imide **I** (3.6 g, 0.01 mole) and 1,3–dibromopropane (7.0 g, 0.03 mole) in acetonitrile (150 ml) was refluxed in the presence of anhydrous K_2CO_3 (4.0 g, 0.03 mole) for 50 h. The inorganic precipitate was filtered off, the solvent was evaporated. Compound **III** was crystallized from octane.

GENERAL PROCEDURE FOR PREPARATION OF N–[4–(4–ARYL–1–PIPERAZYNYL)BUTYL]– OR N–[3–(4–ARYL–1–PIPERAZYNYL)PROPYL]–2'–CHLORODIBENZO[e.h]BICYCLO[2.2.2]OCTANE–2,3– DICARBOXIMIDE [**IV–XI**].

A mixture of compounds **II** or **III** (0.8 g, ~0.02 mmole), anhydrous K_2CO_3 (0.5 g, 3.5 mmole), KI (0.2 g, 1.0 mmole) and the corresponding *N*–substituted piperazine (0.59–0.71 g, 0.04 mmole), was being refluxed in acetonitrile (50 ml) for 50 h. When the reaction was complete, the mixture was filtered and the solvent was evaporated. The residue was crystallized from an appropriate solvent.

RESULTS

This study is a continuation of our research regarding cyclic imides with potential anxiolytic activity considering that we have prepared new derivatives of 2'–chlorodibenzo[e.h]bicyclo[2.2.2] octane–2, 3–dicarboximide. According to our studies, we have selected compounds **IV** and **V** with theoretically the best anxiolytic and antidepressive activity and we have created space models using the Hyper Chem 5.02 software, according to the semiempiric method AM1 to get a better knowledge of their structure. From the chemical point of view, these compounds are the basis for further research in the field of potential drugs, derived from cyclic imides.

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ANTIOXIDATIVE PROPERTIES OF COENZYME Q_{10} AND VITAMIN E IN EXPOSURE TO XYLENE AND GASOLINE AND THEIR MIXTURE WITH METHANOL

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Abstract: Exposure to a mixture of solvents in industry is still a problem particularly in industrial laboratories. In the paint and laquer industry the employees are exposed to xylene (Rx) and gasoline (Rg). The influence of xylene and gasoline or their mixture with methanol on lipid peroxidation was evaluated in the presented paper. Antioxidative properties of CoQ_{10} or vitamin E were also tested. It was observed that xylene caused an increase of lipid peroxidation measured as a MDA level in all used concentrations, but gasoline only in very high doses. The mixture of xylene with methanol increased significantly MDA level, whereas gasoline with methanol did not influence lipid peroxidation. The character of interaction depends on hydrocarbons dose. CoQ_{10} and vitamin E are effective antioxidants lowering the increased MDA level caused by xylene, gasoline or their mixture with methanol, however the dose of CoQ_{10} should be adjusted to the strength of oxidative stress in order to avoid disadvantageous effect. CoQ_{10} is a more effective antioxidant in exposure to xylene rather than gasoline, but vitamin E acts better in exposure to gasoline decreasing the MDA level.

Keywords: xylene, gasoline, methanol, malondialdehyde (MDA), coenzyme Q_{10}, vitamin E, mitochondria.

Free radicals are produced continuously in cells either as by–products of metabolism or leakage from mitochondrial respiration. The most important reaction of free radicals in aerobic cells involve molecular oxygen and its radical derivatives (superoxide anion and hydroxyl radicals), peroxides and transition metals. Cells have antioxidant defense mechanisms to prevent free radical formation and to limit their dama-