*Asian Journal of Chemistry* Vol. 21, No. 9 (2009), 7012-7024

# Adamantane-Containing Biological Active Compounds: Synthesis, Properties and Use

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New biological active adamantane-containing anilides and nitro anilides have been synthesized and studied. The quantum-chemical investigation of these compounds has been carried out. By the semi-empirical method AM1 effective charges on the atoms, bonds lengths and valence angles, enthalpies of formation of initial compounds and probable obtained products of the reaction of nitration of the anilides have been calculated. Based on quantum-chemical calculations and experimental data the direction of the reaction of nitration has been established. The anthelmintic activity and activity towards various microorganisms of the obtained compounds have been studied. The obtained compounds may be recommended as modifier of anthelmintic preparation - phenacetyne, trinoine, diamphenetide, raphoxanide also as a bioactive component for preparation: a) materials with antimycotic properties for prophylaxis and treatment of mycosis and dermatomycosis: adhesive compositions in the form polymer systems; b) protective covers stable to biocorrosion from action some micopathogenic microorganisms.

**Key Words: Adamantane, Anilide, Nitroanilide, Structure, Properties, Bioactivity.**

## INTRODUCTION

At the beginning of 21st century a treatment of population fallen in illness from especially dangerous helminthes (echinococcosis, trichinellosis, fascioliasis, *etc*.) has been becoming an important issue of the day[1-3].

There are many anthelmintic preparations with a wide spectrum of action in a veterinary and medical practice for dehelminthization of animals and human being. Research on derivatives of aminophenoles and salicylic anilides has led to creation of various groups of highly effective anthelmintics (hexiqole, acemidophene, *etc*.)[4,5]. However, during the protracted course of therapy by mentioned above preparations, gradually lose the efficiency owing to successive customary to the helminths. Some of preparations have appeared embryo toxicity, teratogenicity and mutagen properties. Therefore, a research effective anthelmintic preparation is actual problem for modern pharmacology[5].

Modification of various biological active compounds containing -OH and -$NH_2$ groups by O, N-adamantylation and O, N-adamantoylation leads to improvement

of their hydrolytical stability, membranotropic and immunotropic properties[6,7]. Compounds of this type are characterized with minimal therapeutic dose, a high therapeutic index and a wide spectrum of action. According to the aforementioned the modification of existent preparations by lipophilic and membranotropic adamantane radical have a great potential[8].

In many regions of the world some diseases of agricultural plants are widely extended. They are caused by various phytopathogenic microorganisms[9,10]. For example, roots cancer is caused by *A. tunefacicus*. Tumors, halles and nodes are formed as a result of intensive division of affected cells of meristem plant tissues. Roots' and fruit-trees cancers are provoked by - *A. tunefacicus*; a cancer of root crops and beets is provoked by *X. campestris* pv. beticols, *etc*. These diseases distractively damage plants and significantly decrease harvesting efficiency. They also deteriorate quality of grape, water-melons, melons and gourds and other agricultural plants[10]. Adamantane-containing compounds are interesting in this way too[11]. Their complexes with *d*-block transition metal ions have a high biologically activity towards the various phytopathogenic microorganisms[12].

Therefore synthesis of new compounds with high biologically activities as plants protectors and effective means towards phytopathogenic microorganisms, as well as conservators and compounds for antibiocorrosive covers of various natural, synthetic and artificial materials is extremely significant and requires further development[13].

## EXPERIMENTAL

### General procedure

**Synthesis of adamantane-containing anilides:** To the benzene solutions of hydrochlorides of initial amines[7] and basic agents (triethylamine, $NaHCO_3$ or NaOH) was added drop-wise in benzene solution of the chloroanhydride of various carbonic acids (adamantane-1-carboxylic acid, acetic acid, benzoic acid or phenylacetic acid, correspondingly). The mixture was heated and stirred during 1.5-3.0 h. The precipitated crystals were separated by filtration and washed with water. They were dried and physical constants of obtained compounds were determined.

**4-Methoxy-N-(1-adamantoyl)anilide (I):** Yield 90.0 %, m.p. 178-179 ºC, $R_f$ 0.60 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3290 (NH), 3050 (CH, Ar), 2980-2850 (CH, Ad), 1640 (C=O), 1230,1035 (C-O-C). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ = 8.95 (s, 1H), 7.52 (d, *J* 9.1 Hz, 2H), 6.84 (d, *J* 9.1 Hz, 2H), 3.71 (s, 3H), 2.01 (s, 3H), 1.89 (m, 6H), 1.70 (s, 6H); $^{13}C$ NMR (100 MHz, $CDCl_3$): $\delta$ = 175.4, 155.0, 132.3, 121.8, 113.4, 55.0, 40.6, 38.3, 36.0, 27.6.

**4-Ethoxy-N-(1-adamantoyl)anilide (II):** Yield 81.6 %, m.p. 206-207 ºC (ethanol), $R_f$ 0.40 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3290 (NH), 3050 (CH, Ar), 2930, 2908, 2834 (CH, Ad), 1640 (C=O), 1230, 1035 (C-O-C).

**4-(1-Adamantyloxy)acetanilide (III):** Yield 87.0 %, m.p. 167-168 ºC (methanol), $R_f$ 0.50 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3330 (NH), 3100, 3030 (CH, Ar), 2908, 2845 (CH, Ad),1650 (C=O), 1210 (C-O-C).

**4-(1-Adamantyloxy)adamantoylanilide (IV):** Yield 68.0 %, m.p. 240-241 ºC, $R_f$ 0.77 (hexane-diethyl-ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3420 (NH), 2950, 2930, 2850 (CH, Ad), 1670 (C=O), 1210, 1050 (C-O-C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.01 (s, 1H), 7.52 (d, *J* 8.9 Hz, 2H), 6.85 (d, *J* 8.8 Hz, 2H), 2.12 (s, 3H), 2.01 (s, 3H), 1.89 (m, 6H), 1.76 (m, 6H), 1.70 (m, 6H), 1.56 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 175.5, 148.8, 135.0, 124.3, 120.7, 76.5, 42.2, 40.7, 38.3, 35.9, 35.5, 30.1, 27.6.

**4-(1-Adamantyloxy)phenylacetanilide (V):** Yield 61.1 %, m.p. 181-182 ºC, $R_f$ 0.53 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3290 (NH), 3030 (CH, Ar), 2908, 2845 (CH, Ad), 1650 (C=O), 1210 (C-O-C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 10.07 (s, 1H), 7.48 (d, *J* 8.8 Hz, 2H), 7.33 (m, 4H), 7.24 (m, 1H), 87 (d, *J* 8.8 Hz, 2H), 3.60 (s, 2H), 2.10 (s, 3H), 1.75 (m, 6H), 1.55 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 168.6, 148.9, 136.0, 134.9, 128.9, 128.2, 126.4, 124.6, 119.5, 76.6, 43.2, 42.2, 35.5, 30.1.

**4-(1-Adamantyloxy)benzylanilide (VI):** Yield 65.8 %, m.p. 160 ºC, $R_f$ 0.41 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3390 (NH),3050 (CH, Ar), 2908, 2845 (CH, Ad),1650 (C=O), 1230, 1035 (C-O-C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 10.18 (s, 1H), 7.94 (d, *J* 7.0 Hz, 2H), 7.67 (d, *J* 8.8 Hz, 2H), 7.58 (t, J 7.1 Hz, 1H), 7.52 (dd, *J* 7.0 Hz, 2H), 6.94 (d, *J* 8.8 Hz, 2H), 2.13 (s, 3H), 1.79 (m, 6H), 1.57 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 165.2, 149.3, 135.0, 134.8, 131.3, 128.2, 127.5, 124.5, 120.9, 76.7, 42.2, 35.5, 30.1.

**4-(*p*-Chlorophenoxy)-3-chloro-N-(1-adamantoyl)anilide (VII):** Yield 60.4 %, m.p. 176-177 ºC (ethanol), $R_f$ 0.45 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3290 (NH), 3030 (CH, Ar), 2908, 2845 (CH, Ad), 1650 (C=O), 1530 (Cl), 1250 (C-O-C).

**Synthesis of adamantane-containing nitroanilides:** To the solution of adamantane containing anilides in acetic anhydride and acetic acid was added dropwise 56-58 % $HNO_3$. The mixture was cooled on 5-10 ºC and stirred during 0.5-2.0 h. The reaction mixture was dismissing (by pour out on ice water). The precipitated crystals were separated by filtration and washed with $H_2O$; they were dried and physical constants of obtained compounds were determined.

**4-Methoxy-N-(1-adamantoyl)-2-nitroanilide (VIII):** Yield 90.2 %, m.p. 134-135 ºC, $R_f$ 0.65 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3278 (NH), 3090 (CH, Ar), 2908, 2846 (CH, Ad), 1650 (C=O), 1581, 1350 (NO), 1288, 1249 (C-O-C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.62 (s, 1H), 7.65 (d, *J* 9.0 Hz, 1H), 7.49 (d, *J* 3.0 Hz, 1H), 7.30 (dd, *J* 9.0, 3.0 Hz, 1H), 3.83 (s, 3H), 2.02 (s, 3H), 1.88 (m, 6H), 1.70 (m, 6H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 175.6, 155.7, 142.8, 127.3, 125.0, 120.3, 108.8, 55.9, 40.5, 38.2, 35.9, 27.5.

**4-Ethoxy-N-(1-adamantoyl)-2-nitroanilide (IX):** Yield 86.9 %, m.p. 133-135 ºC, $R_f$ 0.73 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, $cm^{-1}$: 3379 (NH), 3090 (CH, Ar), 2930, 2908, 2854 (CH, Ad), 1650 (C=O), 1581, 1350 (NO), 1280, 1056 (C-O-C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.61 (s, 1H), 7.65 (d, *J* 9.0 Hz, 1H), 7.46 (d, *J* 2.9

Hz, 1H), 7.29 (dd, *J* 9.0, 2.9 Hz, 1H), 4.10 (d, *J* 6.9 Hz, 2H), 2.02 (s, 3H), 1.88 (m, 6H), 1.70 (m, 6H), 1.34 (t, *J* 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 175.6, 155.0, 142.7, 127.2, 124.9, 120.7, 109.3, 64.0, 40.5, 38.2, 35.9, 27.5, 14.3.

**4-(1-Adamantyloxy)-2-nitroacetanilide (X):** Yield 65.2 %, m.p. 119-122 ºC, $R_f$ 0.42 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, cm$^{-1}$: 3090 (CH, Ar), 2916, 2854 (CH, Ad), 1650 (C=O), 1350 (NO), 1250 (C-O-C).

**4-(1-Adamantyloxy)-2-nitroadamantoylanilide (XI):** Yield 92.3 %, m.p. 172-174 ºC, $R_f$ 0.86 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, cm$^{-1}$: 3448, 3371 (NH), 3090 (CH, Ar), 2928, 2850 (CH, Ad), 1689 (C=O), 1342 (NO), 1265, 1242 (C-O-C); $^1$H NMR (400 MHz, $CDCl_3$): δ = 9.75 (s, 1H), 7.75 (d, *J* 8.8 Hz, 1H), 7.51 (d, *J* 2.6 Hz, 1H), 7.34 (dd, *J* 8.8, 2.6 Hz, 1H), 2.15 (s, 3H), 2.03 (s, 3H), 1.76 (m, 24H); $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 211.1, 175.8, 130.4, 128.0, 125.8, 120.0, 78.6, 41.9, 40.6, 38.4, 38.1, 35.9, 35.9, 35.3, 30.1, 27.4, 27.3.

**4-(1-Adamantyloxy)-2-nitrophenylacetanilide (XII):** Yield 88.8 %, m.p. 151-153 ºC, $R_f$ 0.80 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, cm$^{-1}$: 3447 (NH); 3090 (CH, Ar), 2915, 2854 (CH, Ad), 1681(C=O), 1342 (NO), 1265, 1234 (C-O-C).

**4-(1-Adamantyloxy)-2-nitrobenzylanilide (XIII):** Yield 59.3 %, m.p. 127-130 ºC, $R_f$ 0.65 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, cm$^{-1}$: 3317 (NH); 3108, 3070 (CH, Ar), 2908, 2854 (CH, Ad), 1697 (C=O), 1334 (NO), 1272, 1234 (C-O-C).

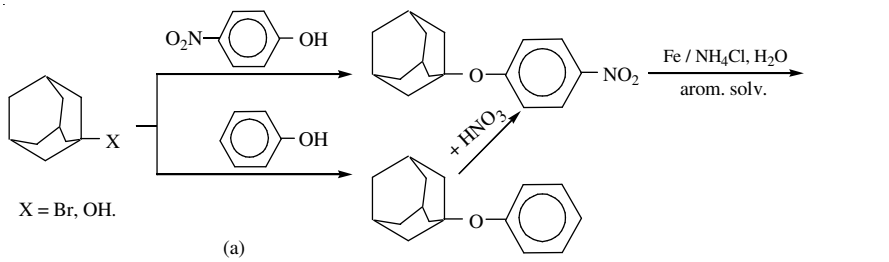
**4-(*p*-Chlorophenoxy)-2-nitro-3-chloro-N-(1-adamantoyl)anilide (XIV):** Yield 90.1 %, m.p. 168-170 ºC, $R_f$ 0.91 (hexane-diethyl ether, 1:1). IR spectra, $\nu_{max}$, cm$^{-1}$: 3290 (NH), 3030 (CH, Ar), 2908, 2845 (CH, Ad), 1650 (C=O), 1530 (Cl), 1342 (NO), 1250 (COC).

IR spectra were obtained with a spectrophotometer Nicollet Nexus 470 machine with MCTB detector[14]. NMR spectra were obtained with an AM-400 (Brucker®) and Talsa BS-467 instrument at an operating frequency of 400 MHz using $CDCl_3$ as a solvent and tetramethylsilane as an internal standard[15]. Mass-spectrograms were obtained with a mass-spectrometer MX-1321A[16], energy of ionized electrons', 70 eV. The reaction course and the purity of the obtained compounds were checked by thin-layer chromatography on silufol UV-254 and alufol plates.

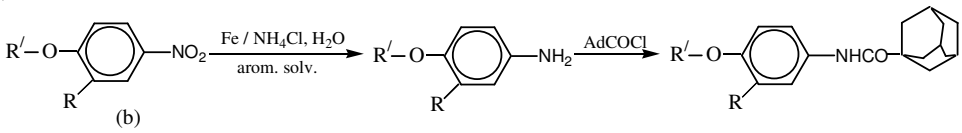
Quantum-chemical calculations were performed on PC with AMD processor with the built-in coprocessor by using Mopac 2000 and CS Chem3D Ultra, v8. We gave the following key-words to guide each computation: EF GNORM = 0.100 MMOK GEO-OK AM1 MULLIK LET DDMIN=0.0 GNORM=0.1 GEO-OK.

## RESULTS AND DISCUSSION

**Synthesis and quantum-chemical investigation of adamantane-containing anilides and nitroanilides:** We synthesized and studied adamantane-containing anilides and nitroanilides with various organic radicals in benzene ring (**Scheme-I**)[17,18]. In order to select of these compounds we considered the availability of their synthesis and possibility of their perspective wide commercialization.




$R^{/}$ = $CH_3$ (III); $R^{/}$ = 1-Ad (IV); $R^{/}$ = Ph (V); $R^{/}$ = $CH_2Ph$ (VI).

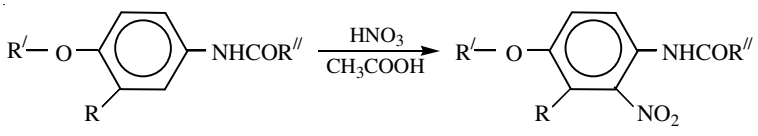



R = H: $R^{/}$ = $CH_3$ (I); $R^{/}$ = $C_2H_5$ (II); R = Cl, $R^{/}$ = y-$ClC_6H_4$ (VII).

**Scheme-I:** Synthesis of some adamantane-containing anilides

Adamantane-containing (Ad) anilides synthesized in two stages according to the **Scheme-I**. The adamantylation of phenols were carried out with 1-adamantanol and 1-bromadamantane and the nitration of the obtained intermediate products. The reduction of the 4-(1-adamantoxy)nitrobenzene with various systems were carried out by molecular hydrogen in presence of Rene's nickel in dry ethanol and ethyl acetate in two-phase system [Fe:$NH_4Cl$:$H_2O$:aromatic solvent (benzene, toluene, xylene); Fe:$CH_3COOH$:$CH_3OH$], by acylation of obtained alkyl(aryl) oxyanilines with carboxylic acid anhydrides and chloro anhydrides in presence of basic agents (triethylamine, NaOH, $Na_2CO_3$ or $CH_3COONa$):

Adamantane-containing nitroanilides were synthesized by nitration of obtained anilides with 56-58 % $HNO_3$ in the media of $CH_3COOH$, at the 5-10 ºC, according to the following general reaction **Scheme-II**:




I-VII VIII-XIV

R=H, $R^{/}$=$CH_3$, $R^{//}$=Ad (VIII); R=H, $R^{/}$=$C_2H_5$, $R^{//}$=Ad (IX); R=H, $R^{/}$=Ad, $R^{//}$=$CH_3$ (X); R=H, $R^{/}$=Ad, $R^{//}$=Ad (XI); R=H, $R^{/}$=Ad, $R^{//}$=Ph (XII); R=H, $R^{/}$=Ad, $R^{//}$=$CH_2Ph$ (XIII); R=Cl, $R^{/}$=y-$ClC_6H_4$, $R^{//}$=Ad (XIV).

**Scheme-II:** Synthesis of some adamantane-containing nitroanilides

The composition and structure of the synthesized compounds (**Schemes I** and **II**) were established by IR, NMR and mass spectral data (Figs. 1, 2a and 2b).

The characteristic absorption bands in IR spectra of the synthesized compounds are as: $\nu_{as}$(NH) (3430-3130 $cm^{-1}$), $\nu_{as}$(C-H) of aromatic ring (3120-3030 $cm^{-1}$), $\nu_{as}$(C-H) of adamantyl group (2910-2830 $cm^{-1}$), $\nu_{as}$(>C=O) carbonyl group (1670-1640 $cm^{-1}$), $\nu_{as}$(NH, C-N) (1540-1500 and 1360-1330 $cm^{-1}$), $NO_2$ (1330-1350 $cm^{-1}$) and C-O-C (1270-1230 $cm^{-1}$) groups[14].

In the $^1$H NMR spectra of the synthesized anilides (Fig. 2a) the singlet signal with chemical shifts within the range 9.01-10.07 ppm for the protons in the NH groups was observed. In the spectra, quartet signals with chemical shifts at 7.30-7.94 ppm for protons in phenyl groups were also visible. In the spectra, multiple signals with chemical shifts at 1.57-2.01 ppm related to the 15 protons in adamantyl groups and the singlet signal with chemical shifts within the range 3.71-3.83 ppm corresponded to three protons in methyl groups (I, VIII) also observed. The singlet signal with chemical shifts 3.60 ppm is related to protons of the methylene group (VI). In the $^1$H NMR spectra of the synthesized nitroanilides (Fig. 2b) one can also observe doublet signal with chemical shifts within the range 7.46-7.51 ppm for the protons $C_{(3)}H$; two doublet signal with chemical shifts within the range 7.29-7.65 ppm is related to protons $C_{(2)}H$ and $C_{(5)}H$. The value of the constant of spin-spin interaction $J$ = 2.8 confirms the substitution of the nitro group in the position 2[15].

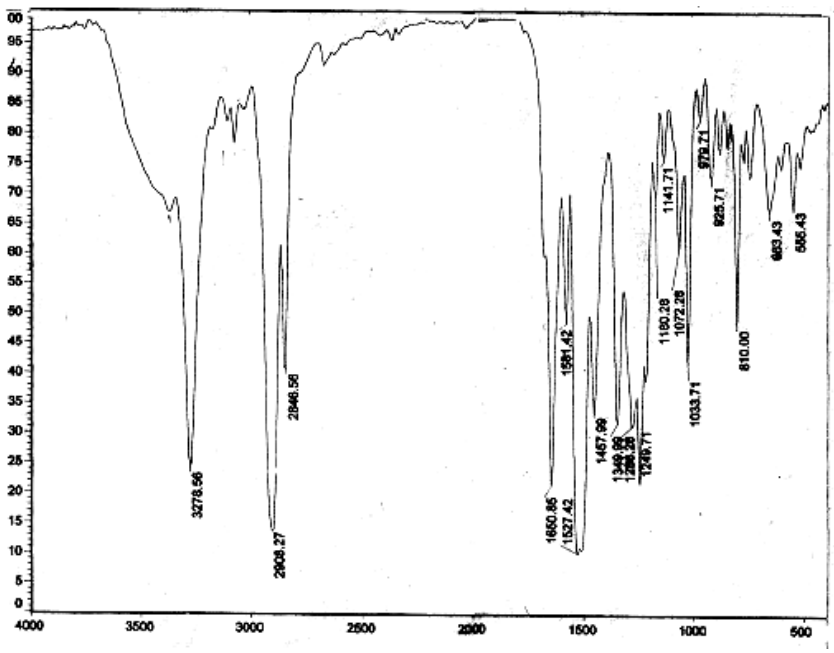



Fig. 1. IR spectrum of 4-methoxy-N-(1-adamantoyl)-2-nitroanilide

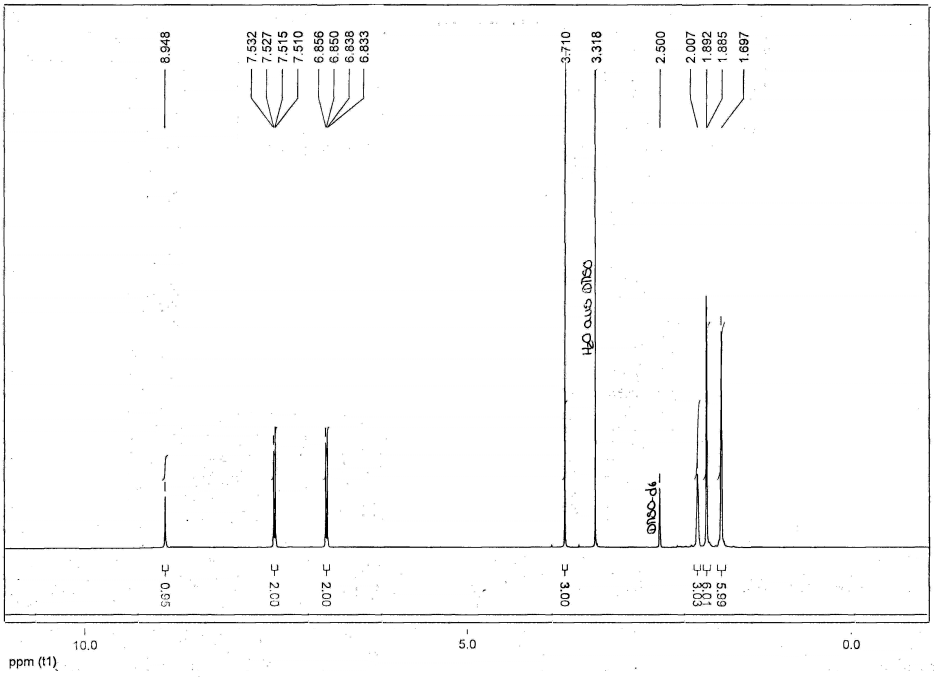



Fig. 2a. $^{1}$H NMR spectrum of 4-methoxy-N-(1-adamantoyl)anilide

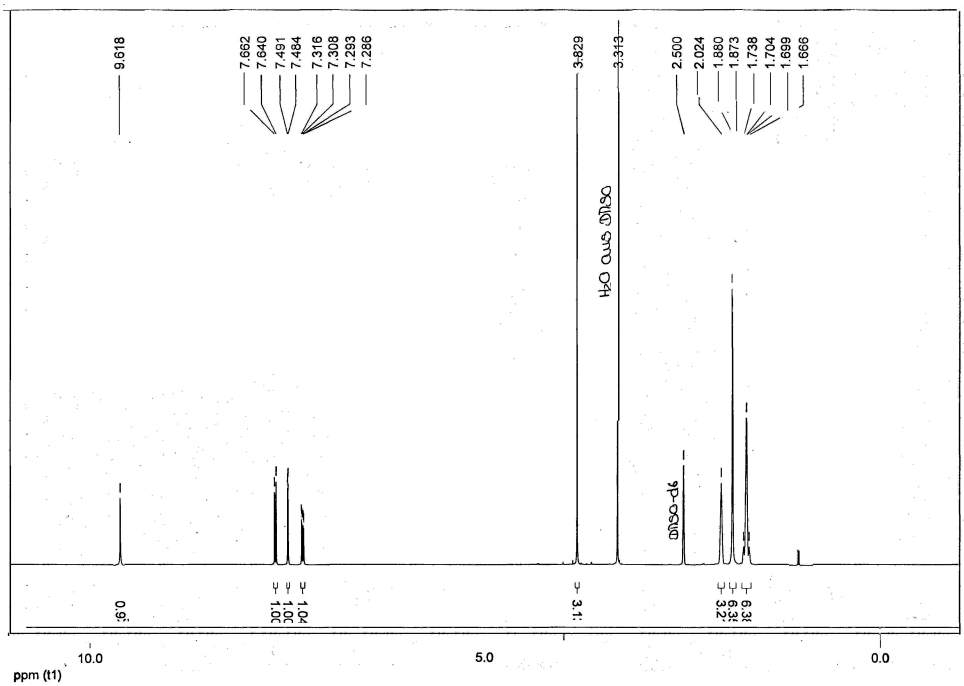
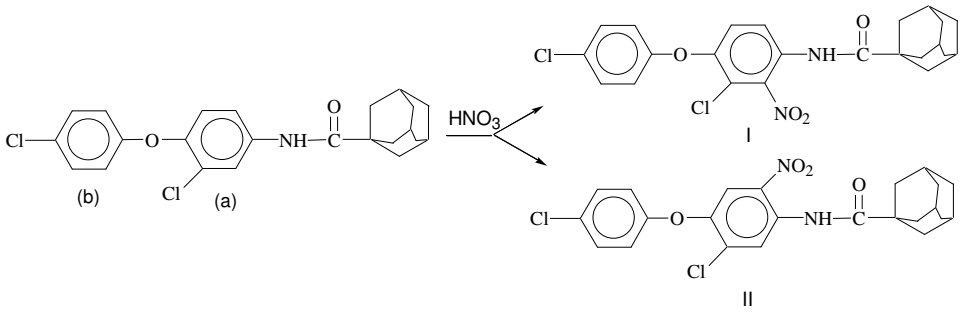



Fig. 2b. $^{1}$H NMR spectrum of 4-methoxy-N-(1-adamantoyl)-2-nitroanilide




**Scheme-III:** Model system of nitration of 4-(*p*-chlorophenoxy)-3-chloro-N-(1-adamantoyl)anilide

In the $^{13}C$ NMR spectra, the signal with four chemical shifts within the range 27.6-40.7 ppm typical for adamantyl group and the chemical shift 55.0 ppm related to the carbon atom of $CH_3$ group (I) were observed. The chemical shifts within the range 165.17-175.57 ppm and the chemical shifts within the range 113.37-155.73 ppm related to carbon atom of C=O groups and carbon atom of phenyl group, correspondingly were also observed.

The mass-spectrogram data for the synthesized anilides and nitroanilides (Table-1) showed that the masses of molecular ($M^+$) and fragmental ions correspond with obtained structures of aforementioned compounds (**Schemes I** and **II**).

TABLE-1
MASS-SPECTRAL DATA FOR SOME SYNTHESIZED ANILIDES AND NITROANILIDES

| Compounds* | Data of mass-spectra, m/z ($I_{rel.}$, %) |
|---|---|
| **I** | 285.2 [$M^+$] (75), 257.2 (6), 214.1 (2.4), 200.1 (13.7), 149.0 (5.4), 135.1 (100) |
| **IV** | 330.2 [$M^+$] (18.7), 284.2 (3.6), 210.1 (1.8), 135.1 (100) |
| **VIII** | 405.2 [$M^+$] (10.1), 255.2 (13.7), 212.1 (1.8), 135.1 (100) |
| **XI** | 450.3 [$M^+$] (8.1), 316.1 (1.8), 270.2 (1.8), 227.2 (1.7), 152.1 (1.9), 135.1 (100) |

*__Schemes__ I and **II**

As the initial anilides containing several feasible reaction centers, a series of quantum-chemical calculations were performed by using CS MOPAC (Chem3D Ultra-version 8.03, method AM1 - Austin Model 1)[19,20] to establish the direction of the reaction of nitration (**Scheme-I**). The heat of formations (enthalpy, $\Delta H_f$) and reaction heat effects ($\Delta H_{reac.}$) for probable reaction products were also calculated. As a model reaction, the nitration of 4-(*p*-chlorophenoxy)-3-chloro-N-(1-adamantoyl)anilide (AH) was selected.

The 3D model of the optimized structure of 4-(*p*-chlorophenoxy)-3-chloro-N-(1-adamantoyl)anilide is given in Fig. 3.

The valence angles between carbon atoms in benzene ring of the 4-(*p*-chloro phenoxy)-2-nitro-3-chloro-N-(1-adamantoyl)anilide (118-120°) were calcualted which corresponds to the $sp^2$-hybridization state of carbon atoms in same arene systems[18].

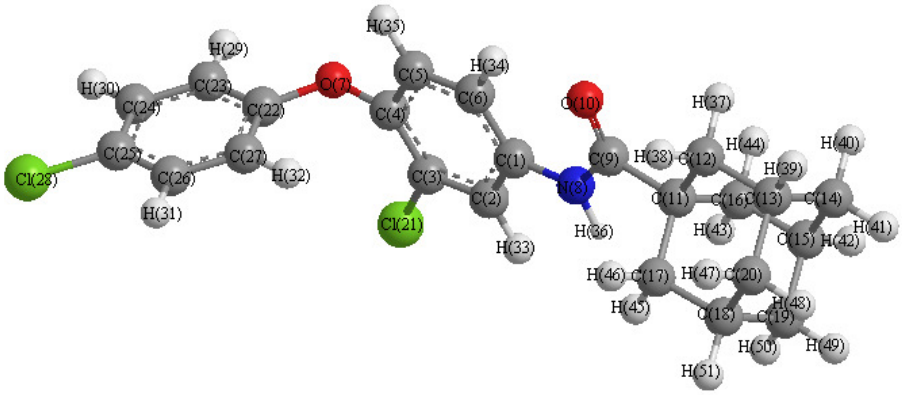



Fig. 3. 3D model of 4-(*p*-chlorophenoxy)-3-chloro-N-(1-adamantoyl)anilide

The quantum-chemical calculations show that in benzene ring (a) the value of effective charges (Table-2) at $C_{(2)}$ and $C_{(6)}$ carbon atom are -0.23315 and -0.20288, correspondingly. During the reaction of nitration, the $NO_2^+$ group attacks $C_{(2)}$ carbon atom. The results of the calculation show that formation of the product I ($\Delta H_f$ = -175.60 kJ/mol) is slightly more probable than the product II (**Scheme-III**) ($\Delta H_f$ = -166.90 kJ/mol) (for the initial anilide [4-(*p*-chlorophenoxy)-3-chloro-N-(1-adamantoyl)anilide] $\Delta H_f$ = -220.16 kJ/mol).

TABLE-2
EFFECTIVE CHARGES ON THE CARBON ATOMS IN THE MOLECULE OF 4-(*p*-CHLOROPHENOXY)-3-CHLORO-N-(1-ADAMANTOYL)ANILIDE

| Atoms | Charge | Atoms | Charge | Atoms | Charge | Atoms | Charge |
|---|---|---|---|---|---|---|---|
| C(1) | 0.10404 | C(9) | 0.38497 | C(16) | -0.22828 | C(23) | -0.18751 |
| C(2) | **-0.23315** | C(11) | -0.08632 | C(17) | -0.23910 | C(24) | -0.16605 |
| C(3) | -0.04126 | C(12) | -0.23775 | C(18) | -0.16030 | C(25) | -0.08462 |
| C(4) | 0.03545 | C(13) | -0.16102 | C(19) | -0.24526 | C(26) | -0.16718 |
| C(5) | -0.16977 | C(14) | -0.24443 | C(20) | -0.24527 | C(27) | -0.19257 |
| C(6) | **-0.20288** | C(15) | -0.16405 | C(22) | 0.05010 | | |

The calculated activation energy of the obtained nitroanilides shows that the minimal activation energy (71.2 kJ/mol) corresponds to nitroanilide obtained by nitration in 2-position (ring a). For position 6 activation energy is 100.8 kJ/mol (**Scheme-III**).

It has been established that the reaction of nitration of benzene ring (b) has lower probability than the reaction of nitration of benzene ring (a). Activation energies for identical positions in benzene ring (b) are 98.4 kJ/mol and 104.7 kJ/mol, corres-pondingly. Reaction of nitration in this position takes place only in rigid condition (in the media of concentrated $H_2SO_4$, at the18-20 ºC) in comparison with reaction of nitration of benzene ring (a). The obtained results are in accordance with the NMR spectral data of the corres-ponding product[7,12].

By the AM1 method, the heat of formation of AH, its nitro compounds and intermediate products (complex of AH with nitrating mixture) were also calcualted. The reaction of nitration of AH described by following scheme:

$$AH + NO_2^+ + HSO_4^- \longrightarrow A\text{-}NO_2 + H_2SO_4$$

The initial distance ($R_{CN}$) between carbon atom and nitrogen atom of nitronium ion in AH was 2.50 Å. The approach of $NO_2^+$ to molecule of AH was realized by step equal to 0.05 Å. In the hydrosulphate-anion the distance between the oxygen atom and substituted hydrogen atoms of AH molecule decreased synchronously with the changing of $R_{CN}$.

The dependence of the changes of enthalpy ($\Delta H_f$) on $R_{CN}$ showed that in both cases the character of the changing of $\Delta H_f$ is the same (Figs. 4 and 5).

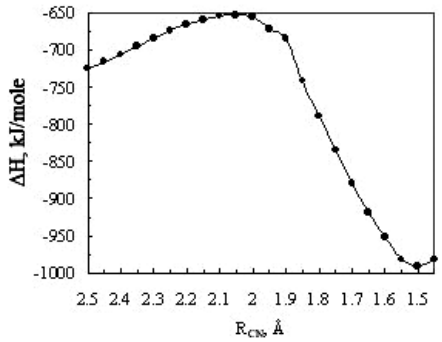



Fig. 4. Dependence of enthalpy ($\Delta H_f$) on the reaction coordinates ($R_{CN}$) for 6-nitroanilide

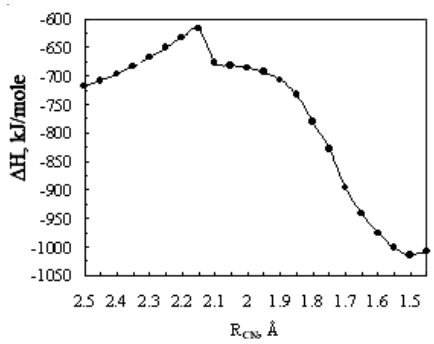



Fig. 5. Dependence of enthalpy ($\Delta H_f$) on the reaction coordinates ($R_{CN}$) for 2-nitroanilide

**Study of bioactive properties of adamantane-containing anilides and nitroanilides:** The anthelmintic properties and biological activity of adamantane-containing anilides and nitroanilides towards different microorganisms were also tested.

The fasciolocide activity[18] of obtained compounds from anilide series I-VII on artificial fallen in illness (*Fasciola hepatica*) of experimental animals (white rats) was also studied (Tables 3 and 4). It is established that synthesized compounds in dose 65, 150 and 200 mg/kg in the form of suspension have sufficiently high activity-intensive efficiency (IE) 60 and 80 %, extensive efficiency (EE) - 80 and 90 %, correspondingly (Table-3)[18].

The anthelmintic activity (fascioliasis, strongyliatosis and triqocefalosis) of some of the alkoxyanilides (**Scheme-I**, **I-VII**) on sheeps (Table-5) were also tested. As Table-5 shows 4-methoxy-N-(1-adamantoyl)anilide has the best polyhelmitic activity (80-100 %). At the same time, the used compounds did not have the poisonous action on the experimental animals.

Biological activity of adamantane-containing anilides and nitroanilides towards different microorganisms were performed by using known procedures[18,21]. The biocidal properties of compounds **I**, **VIII** and **IX** (**Schemes I** and **II**) have also tested.

TABLE-3
RELATION EFFICIENCY OF COMPOUNDS **I**, **II**, **III**, **IV**, **V** AND HEXIQOLE BY RATS' FASCIOLIASIS

| Test groups | Animals number in group | Animals middle mass | Preparation | Dose (mg/kg and form) | Number of days after ill | Determination of effectivity by method of dissection | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Healing animals | EE (%) | Discovery fasciole middling in heart | IE (%) |
| Exp. | 5 | 224 | I | 200, bolus | 60 | 2 | 40 | 14 | 46.15 |
| – | 4 | 312 | II | 65, bolus | 60 | 3 | 75 | 0.25 | 90.4 |
| – | 5 | 265 | II | 200, bolus | 60 | 2 | 40 | 1.6 | 38.4 |
| Std. | 5 | 266 | – | – | 60 | 0 | 0 | 2.6 | 0 |
| Exp. | 5 | 105 | II | 200, suspension | 54 | 2 | 40 | 0.6 | 76.9 |
| – | 5 | 92 | I | – | 54 | 2 | 40 | 1.0 | 61.5 |
| – | 5 | 92 | II | – | 54 | 2 | 40 | 1.0 | 61.5 |
| – | 5 | 95 | I | 200, Curd's paste | 54 | 2 | 40 | 1.0 | 61.5 |
| – | 5 | 95 | II | – | 54 | 5 | 100 | 0 | 100 |
| Std. | 5 | 96 | – | 65, suspension | 54 | 0 | 0 | 2.6 | 0 |
| Exp. | 3 | 260 | III | 65, bolus | 57 | 0 | 0 | 3.3 | 37.7 |
| – | 3 | 290 | IV | – | 57 | 2 | 66 | 2.3 | 56.6 |
| – | 3 | 256 | V | – | 57 | 2 | 66 | 2.3 | 75.4 |
| – | 3 | 260 | Hexiqole | 200, bolus | 57 | 3 | 100 | 0 | 100 |
| Std. | 3 | 270 | – | – | 57 | 0 | 0 | 5.3 | 0 |
| Exp. | 3 | 303 | II | 200, bolus | 35 | 0 | 0 | 4.0 | 20 |
| – | 3 | 313 | V | – | 35 | 0 | 0 | 2.0 | 60 |
| Std. | 3 | 305 | – | – | 35 | 0 | 0 | 5.0 | 0 |

TABLE-4
RELATION EFFICIENCY OF COMPOUNDS **II**, **III**, **IV**, **V**, **VII** AND PHENACETYNE BY RATS'FASCIOLIASIS

| Test groups | Animals number in group | Animals middle mass | Preparation | Dose (mg/kg and form) | Number of days after ill | Determination of effectivity by method of dissection | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Healing animals | EE (%) | Discovery fasciole middling in heart | IE (%) |
| Exp. | 5 | 70 | II | 150, suspension | 13 | 3 | 60 | 0.4 | 80 |
| – | 5 | 70 | III | – | 13 | 3 | 20 | 2.4 | 30 |
| – | 5 | 70 | III | – | 13 | 0 | 0 | 0.18 | 91 |
| Std. | 5 | 66 | – | – | 13 | 0 | 0 | 2 | – |
| Exp. | 5 | 86 | V | 150, suspension | 20 | 1 | 20 | 1.6 | 20 |
| – | 5 | 68 | VII | – | 20 | 4 | 80 | 0.2 | 90 |
| – | 5 | 70 | Phenacetine | – | 20 | 4 | 80 | 0.8 | 90 |
| Std. | 5 | 68 | – | | 20 | 0 | 0 | 2.0 | 0 |
| Exp. | 3 | 283 | IV | 200, bolus | 25 | 0 | 0 | 3.0 | 34 |
| – | 3 | 305 | V | – | 25 | 0 | 0 | 4.0 | 20 |
| Std. | 3 | 305 | – | – | 25 | 0 | 0 | 5.1 | 0 |

TABLE-5
ANTHELMINTIC ACTIVITY OF
4-METHOXY-N-(1-ADAMANTOYL)ANILIDE (SHEEP)

| Compound | Dose (mg/kg) | Helminth-scopy (%) | | Dissection (%) | |
|---|---|---|---|---|---|
| | | EE | IE | EE | IE |
| I | 100 | | | | |
| Fascioliasis | | 80.0 | 98.5 | 66.5 | 70.5 |
| Strongyliatosis | | 80.0 | 99.7 | 66.6 | 99.7 |
| Triqocefalosis | | 100.0 | 100.0 | 100.0 | 100.0 |

As test cultures we have selected the fungi *Fusarium proliferatum* and *Agrobacterium tumefaciens* (on the basis of buter-penton agar). The testing results showed that the compound **IX** have relative high activity in comparison to compound **VIII** and at the concentrations 0.01 and 0.1 g/L neutralizes *Fusarium proliferatum* (the zones of neutralization equal to 1.5 ± 0.064 and 1 ± 0.04 mm, correspondingly). Compound **I** at the concentration 0.1 g/L reveals relative high activity towards to *Agrobacterium tumefaciens* (zone of neutralization equal to 2 ± 0.04 mm).

Based on the preliminary investigations, it is established that the present compounds may be recommended as modification anthelmintic preparation-phenacetyne, trinoine, diamphenetide, raphoxanide also as a bioactive component for preparation: a) materials with antimycotic properties for prophylaxis and treatment of mycosis and dermatomycosis: adhesive compositions in the form polymer systems for nail fungi diseases treatment; b) protective covers (film materials and impregnating compositions) stable to biocorrosion from action some micropathogenic micro-organisms[21,22].

## ACKNOWLEDGEMENTS

The authors thanks Prof. Dr. Uli Kazmaier (University of Saarland, Institute of Organic Chemistry), Dr. Davit Zurabishvili and Dr. Iuri Sadaterashvili for their encouragement.

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(*Received*: 27 November 2008; *Accepted*: 30 March 2009) AJC-7725