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SYNTHESIS AND ANTICONVULSIVE ACTIVITY OF NEW 1,3-DIAZAADAMANTANE DERIVATIVES

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The work is devoted to the synthesis and study of the neurotropic activity of some derivatives of 3,7-diazabicyclo/3.3.1/nonanes. For this, various 5,7-dialkyl, methylphenyl, diphenyl 1,3-diazaadamantanes **1** were synthesized, which, upon interaction with acid chlorides of aliphatic, aromatic and heterocyclic acids, were converted into the corresponding 3,7-diazabicyclo/3.3.1/nonanes. The anticonvulsant activity of the synthesized compounds was studied. Among them, substances with pronounced anticorazole activity were identified.

References 7.

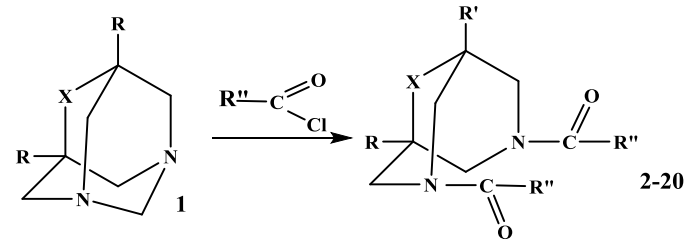
Thanks to recent advances in molecular biology, our understanding of the nature of memory impairments, the processes underlying brain aging, and the disorders that occur during brain injuries and strokes has significantly expanded, which has made it possible to more purposefully approach the search for new means of correcting these disorders.

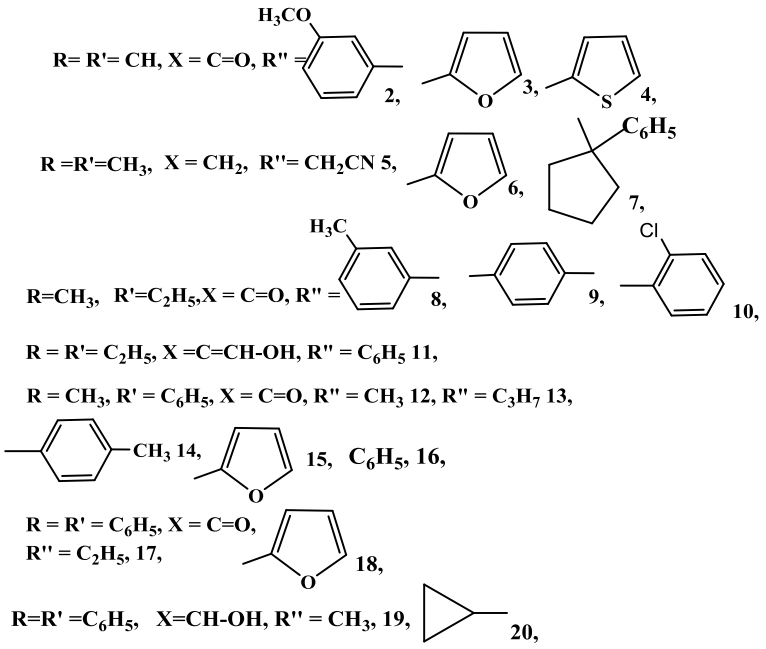
It has been shown that some adamantane derivatives, in particular, memantine hydrochloride (1-amino-3,7-dimethyladamantane), amantadine, are widely used in the treatment of Alzheimer's and Parkinson's diseases [1-3]. Derivatives of 1,3-diazaadamantane differ from adamantane derivatives by the presence of two nitrogen atoms in the framework of the molecule and may have similar pharmacological activity. Previously, we synthesized some 1,3-diazaadamantane compounds with anticonvulsant activity [5].

The aim of this work is a comparative study of the neurotropic activity of some derivatives of 1,3-diazaadamantanes, in particular 3,7-diazabicyclo/3.3.1/nonanes. To obtain these compounds, various 5,7-diakyl-,

methyl-phenyl-, diphenyldiazaadamantanes **1** were synthesized [6], which were converted into the corresponding 3,7-diazabicyclo/3.3.1/nonanes by reactions with aliphatic, aromatic, carbocyclic acid chlorides. nonanes **2-20**. The synthesis was carried out according to Scheme .

Scheme





The structure of the synthesized compounds was confirmed by elemental analysis data of IR, ^{1}H and ^{13}C NMR spectra.

The study of the anticonvulsant activity of compound **2-20** was carried out on 50 white mice weighing 18-24 *g* of both sexes.

The effect of compounds on corazole convulsions induced by subcutaneous administration of corazole at a dose of 90 *mg*/*kg* was studied. Side neurotoxic effects were judged by the phenomena of myorelaxation, violation of the coordination of movement, using the test. "rotating rod"[7]. When analyzing the data, it was found that all compounds exhibit anticonvulsant activity to one degree or another. Compounds 1-methyl-5-ethyl-9-oxo-3,7-di-(1-chlorophenylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**10**), 1-methyl-

5-phenyl-9-oxo-3,7-di-(4'-methylphenylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**14**), 1-methyl-5-phenyl-9-oxo-3,7- x`(dipropylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**13**), 1,5-difenyl-9-oxo-3,7-di-(furylcarbonyl)-3,7-diazabicyclo/3.3.1./nonane (**18**), 1-methyl-5-phenyl-9-oxo-3,7-di-(furyl)-3,7-diazabicyclo/3.3.1/nonane (**15**) prevent corazole convulsions in 40% of experimental animals. Compounds 1,5-dimethyl-9-oxo-3,7-di-(3'-methoxyphenylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**2**), 1,5-dimethyl-3,7-(1'-phenylcyclopentylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**7**), 1,5-diphenyl-9-hydroxy-3,7-di-(cyclopropanecarbonyl)-3,7-diazabicyclo/3.3.1./nonane(**20**) prevented corazole convulsions in 20% of experimental mice. The rest of the compounds have no neurotoxic effect at the studied doses.

Experimental part

IR spectra were recorded in vaseline oil on a Nicolet Avatar 330 FT-IR spectrophotometer; ^{1}H and ^{13}C NMR spectra were recorded on a Varian Mercury-300 instrument (300 *MHz*) in DMSO-d_6/CCl_4, 1/3, internal standard TMS. The progress of the reaction and the purity of the substances were monitored by TLC on "Silufol UV-254" plates in propanol-water systems, 7:3. Melting points were determined on a "Boetius" apparatus.

General procedure for the preparation of 2-20. To 10 *mmol* of **1** in a mixture of 100 *m* benzene, 30 *ml* of water and 50 *mmol* of $NaHCO_3$, benzene 25 *mmol* of the corresponding acid chloride is added dropwise with stirring at room temperature. After all the acid chloride has been added, stir for a further 2 *hours* (TLC monitoring). Then the benzene layer is separated, washed with water, dried over $MgSO_4$ and distilled off. The residue is recrystallized from isopropanol.

1,5-Dimethyl-9-oxo-3,7-di-(3'-methoxybenzoyl)-3,7-diazabicyclo/3.3.1/nonane (2). Prepared from 1.8 *g* (10 *mmol*) of 5,7-dimethyl-6-oxo-1,3-diazaadamantane (**1**) and 3.41 *g* (20 *mmol*) of *m*-methoxybenzoyl chloride. Yield 2.70 *g* (62*%*), R_f 0.80, mp. 213-253 *°C*. IR spectrum, ν, cm^{-1}: 1634 (C=Carom), 1729 (C=O). ^{1}H NMR spectrum, (300 *MHz*, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.94 (6H, s, 2 × CH_3); 3.00 (2H, br. d, *J* = 13.7, CH_2); 3.36 (2H, br. d, *J* = 12.9, NCH_2); 3.85 (6H, s, 2 × OCH_3); 3.91 (2H, br.d, *J* = 12.9, NCH_2); 4.80 (2H, br. d, *J* = 13.7, NCH_2); 6.92-6.98 (4H, m, 2H-4.6, C_6H_4); 7.08 (2H, dd, *J* = 2.4, 1.4, 2H-C_6H_4); 7.31 (2H, dd, *J* = 8.2, 7.6,C_6H_4);. ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 16.2 ($2CH_3$); 45.3 (2C); 52.0 (2×C); 54.7 (2×OCH_3); 58.5 (w. s); 111.9 (2×CH); 115.3 (2×CH); 118.6 (2CH); 128.7 (2CH); 136.6 (2C); 158.9 (2×C); 169.1(2×CO); 210.6 (CO). Found,*%*: C 68.87; H 6.48; No. 6.37. $C_{25}H_{28}N_2O_5$. Calculated,*%*: C 68.80; H 6.42; N. 6.42.

1,5-Dimethyl-9-oxo-3,7-di-(2'-furancarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**3**)**.** Prepared from 1.8 *g* (10 *mmol*) of 5,7-dimethyl-6-oxo-1,3-diazaadamantane (**1**) and 2.61 *g* (20 *mmol*) of furan-2-carboxylic acid Cl-anhydride. Yield 2.3 *g* (65%), R_f 0.78, mp. 220-221 °C. IR spectrum, ν, cm^{-1}: 1565 (fur); 1610, 1629 (truck), 1720 (C=O); 3098 (truck). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J*, *Hz*): 1.01 (6H, s, 2 × CH_3); 3.41 (4H, br. s, 2 × NCH_2); 4.62 (4H, br.s, 2 × NCH_2); 7.02 (2H, dd, *J* = 3.3, 1.6, 2H-4fur); 7.38 (2H, dd, *J* = 3.3, 1.6, H-5fur); 7.48 (2H, dd, J = 3.3,1.6, 5fur). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 16.1 ($2CH_3$); 45.7 (4×NCH_2); 66.1 (2×C); 126.9 (2×C-4-truck); 128 (2×C-3-trucks); 129 (2×C-5, truck); 136.2; 162.5; 210.4 (CO). Found,%: C 59.11; H 5.66; N 7.91. $C_{19}H_{20}N_2O_5$. Calculated,%: From 59.06; H 5.62; N 7.86.

1,5-Dimethyl-9-oxo-3,7-di-(2'-thiophenecarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**4**)**.** Prepared from 1.8 *g* (10 *mmol*) of 5,7-dimethyl-6-oxo-1,3-diazaadamantane (**1**) and 3.68 *g* (25 *mmol*) of thiophenecarboxylic acid Cl anhydride. Yield 2.2 *g* (57%), R_f 0.42, mp. 205-206 °C. IR spectrum, ν, cm^{-1}: 1522; 3103; 3081 (thiophene); 1719 (C=O). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J*, *Hz*): 1.02 (6H, s, 2 × CH_3); 3.42 (4H, br. s, 2 × NCH_2); 4.64 (4H, br.s, 2 × NCH_2); 7.05 (2H, dd, *J* = 3.5, 1.6, 2H-3 thiophene); 7.36 (2H, d, *J* = 3.3, H-4 thiophene); 7.49 (2H, dd, *J* = 3.5, 5 thiophene). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 16.1 ($2CH_3$); 45.7; 53.2; 58.3; 125.9; 128.7; 129.1; 136.7; 162.5; 210.4 (CO). Found,%: C 58.70; H 5.20; N 7.26; S 16.42. $C_{19}H_{20}N_2O_2S_2$. Calculated,%: C 58.76; H 5.15; N 7.21; S 16.49.

1,5-Dimethyl-9-oxo-3,7-di-(cyanocarbonyl)-3,7-diazabicyclo/3.3.1/-nonane (**5**)**.** Obtained from 1.8 *g* (10 *mmol*) 5,7-dimethyl-6-oxo-1,3-diazaadamantane (**1**) and 2.31 *g* (20 *mmol*) Cl-anhydride cyanoacetic acid. Yield 1.2 *g* (40%) and b 1.7 *g* (56%), R_f 0.71, mp. 256-266 °C. IR spectrum, *ν, cm*$^{-1}$: 1675, 1720 (C=O); 2259 (C≡N). ^{1}H NMR spectrum, (300 *MHz*, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.92 (6H, br. s, 2 × CH_3); 2.84 (2H, br. d, *J* = 12.5, NCH_2); 3.2-3.26 (2H, m, NCH_2); 3.88-4.1 (6H, m, 3×NCH_2); 4.82 (2H, brd, *J* = 12.5, NCH_2). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 15.2 ($2CH_3$); 25.2 (2×CH_2CN); 45.2 (2×CH_2); 54.2 (2×C); 55.9 (2×C); 115.4(C); 162.2 (2C); 208 (CO). Found,%: C 45.35; H 4.58; N 18.48. $C_{15}H_{18}N_4O_3$. Calculated,%: From 45.30; H 4.53; N 18.54.

1,5-Dimethyl-3,7-di-(2'-furancarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**6**)**.** Obtained from 1.66 *g* (10 *mmol*) of 5,7-dimethyl-6-oxo-1,3-diazaadamantane (**1**) and 2.61 *g* (20 *mmol*) of Cl-anhydride of furan-2-carboxylic acid. Yield 2.1 *g* (63%), R_f 0.78, mp. 164-165 °C IR spectrum, ν, *cm*$^{-1}$: 1565, 1629 (furyl); 1610, (furyl), 3098 (furyl). ^{1}H NMR spectrum, (300 *MHz*, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.98 (6H, s, 2 × CH_3); 1.46 (2H, s, CH_2); 2.84 (4H, br.s, 2 × NCH_2); 4.30 (4H, very br. s, 2×NCH_2); 6.42 (2H, s, 2H-4fur); 6.86

(2H, dd, J = 3.3, 2H-3fur); 7.48 (2H, s, 2H-5fur). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 24.5 ($2CH_3$); 30.5 (CH_3); 46.4, 52.7 (2×C); 110.4 (2C-truck); 114.7 (2C-truck); 142.6 (2C-truck); 147.6 (2C-truck); 157.9 (CO). Found,*%*: C 68.31; H 6.63; N 8.32. $C_{19}H_{22}N_2O_4$. Calculated,*%*: C 68.28; H 6.57; N 8.38.

1,5-Dimethyl-3,7-di-(1'-phenylcyclopentylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**7**)**.** Prepared from 1.66 *g* (10 *mmol*) of 5,7-dimethyl-6-oxo-1,3-diazaadamantane (**1**) and 4.17 *g* (20 *mmol*) of 1-phenylcyclopentylcarboxylic acid Cl anhydride. Yield 2.5 *g* (52*%*), R_f 0.71, mp. 256-266 *℃*. IR spectrum, *ν, cm*$^{-1}$: 1619 (arom), 1731, 1932 (C=O); 3055 (cyclopropane). ^{1}H NMR spectrum, (300 *MHz*, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.64 (6H, s, 2 × CH_3); 1.05 (2H, s, NCH_2); 1.35 1.58 . (6H, m), 1.65–1.88 (6H, m), 1.92–2.05 (2H, m), 2.24 (2H, br.l, *J* = 13.3), 2.39–2.51 (2H, m), 2.60–2.71 (2H, m), 3.21 (2H, br. d, *J* = 13.3, 12 CH_2) and 4.26 (2H, br. d, *J* = 13.3); 7.02-7.08 (4H, m, 2H-2, 2'ph); 7.09-7.16 (2H, m, 2H, 4H ph); 7.21-7.29 (4H, m, 2H, 3'ph). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 24.5, 24.7, 25.9, 30.0, 34.2, 42.1, 45.8, 51.5, 55.5, 57.5, 124.2, 125.2, 128.1, 145.2, 1 73.4. Found, *%*: C 79.08; H 8.69; N 5.21. C32H42N2O2. Calculated, *%*: From 79.02; H 8.64; N 5.76.

1-Methyl-5-ethyl-9-oxo-3,7-di-(3'-methylbenzoyl)-3,7-diazabicyclo/3.3.1/nonane (**8**)**.** Prepared from 1.94 *g* (10 *mmol*) of 5-methyl-7-ethyl-6-oxo-1,3-diazaadamantane (**1**) and 3.08 *g* (20 mmol) of *m*-methylbenzoyl chloride. Yield 2.6 *g* (62%), R_f 0.80, mp. 187-188 *℃*. IR spectrum, ν, *cm*$^{-1}$: 1602 (C=Carom), 1642.1729 (C=O). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.83 (2H, t, *J* = 7.5, CH_3CH_2); 0.93 (3H, s, CH_3); 1.40-1.56 (2H, m, CH_2CH_3); 2.43 (6H, s, 2 × CH_3-arom); 2.99 (2H, br. s), 3.33 (2H, br. s), 3.94 (2H, br. s), and 4.79 (2H, br. s, 4 × CH_2); 7.20 - 7.33 (8H, m, 2H×C_6H_4). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 7.1(CH_3), 16.2(CH_3), 20.9($2CH_3$); 23.3 (CH_2); 45.3, 50.1 (br.s), 53.0 (br.s), 58.5 (br.s), 135.3, 137.0, 169.4 (NCO), 210 (CO). Found, *%*: C 74.70; H 7.24; N. 6.63. $C_{26}H_{30}N_2O_3$. Calculated, *%*: C 74.64; H 7.17; N 6.69

1-Methyl-5-ethyl-9-oxo-3,7-di-(4'-methylbenzoyl)-3,7-diazabicyclo/3.3.1/nonane (**9**)**.** Prepared from 1.94 *g* (10 *mmol*) of 5-methyl-7-ethyl-6-oxo-1,3-diazaadamantane (**1**) and 3.08 *g* (20 *mmol*) of 4-methylbenzoyl chloride. Yield 2.7 *g* (65%), R_f 0.33, mp. 138-139 *℃*. IR spectrum, ν, *cm*$^{-1}$: 1602 (C=Carom), 1642.1719 (C=O). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.83 (3H, t, *J* = 7.5, CH_3CH_2); 0.95 (3H, s, CH_3); 1.38-1.56 (2H, m, CH_2CH_3); 2.40 (6H, s, 2 × CH_3-arom); 2.98 (2H, br. s), 3.07 (2H, br. s), 3.96 (2H, br. s), and 4.74 (2H, br. s, 4 × CH_2N); 7.21 (4H, d, J = 5.9, C_6H_4); 7.38 (4H, d, *J* = 5.9, C_6H_4). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 7.2 (CH_3), 16.2 (CH_3), 20.8 ($2CH_3$); 23.3 (CH_2); 45.4; 47.6; 51.1 (br.s), 53.1 (br.s), 56.7 (br.s), 58.7 (br.s); 128.2 (CH); 128.2 (CH); 132.4

(CH); 138.5 (CH); 169.3 (N-CO), 210.9 (CO). Found, *%*: C 74.58; H 7.12; No. 6.64. $C_{26}H_{30}N_2O_3$. Calculated, *%*: C 74.64; H 7.17; N 6.69

1-Methyl-5-ethyl-9-oxo-3,7-di-(2'-chlorobenzoyl)-3,7-diazabicyclo/3.3.1/nonane (**10**)**.** Prepared from 1.94 *g* (10 *mmol*) of 5-methyl-7-ethyl-6-oxo-1,3-diazaadamantane (**1**) and 3.48 *g* (20 *mmol*) of 2-Cl-benzoyl chloride. Yield 2.8 *g* (61*%*), R_f 0.33, mp. 197-198 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1620 (C=Carom), 1645.1724 (C=O). ^{1}H NMR spectrum, (300 *MHz*, $CDCl_3$) δ, ppm, (*J, Hz*): 0.80 (3H, t, *J* = 7.6, CH_3CH_2); 0.94 (3H, s, CH_3); 1.37-1.60 (2H, m, CH_2CH_3); 3.02 (2H, dt, NCH_2); 3.34-3.41 (2H, m, NCH_2); 3.58-3.68 (2H, m, NCH_2); 4.79 (2H, ddd, *J* = 13.8, 5.0, 2.4, NCH_2); 7.40-7.50 (6H, m) and 7.67-7.73 (2H, ppm, 2 × C_6H_4Cl). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 7.0, 16.0, 23.1, 44.97, 45.03, 47.2, 50.2, 52.3, 55.0, 57.0, 127.1, 128.6, 128.8, 128.9, 1 29.4, 129.9, 134.7, 166.5, 209.8. Found, *%*: C 62.80; H 6.32; N 6.14.; Cl 15.51; $C_{26}H_{24}N_2Cl_2O_3$. Calculated, *%*: C 62.74; H 6.17; No. 6.10; Cl 15.46.

1,5-Diethyl-9-hydroxy-3,7-di-(benzoyl)-3,7-diazabicyclo/3.3.1/nonane (**11**). Prepared from 2.1 *g* (10 *mmol*) of 5,7-diethyl-6-hydroxy-1,3-diazaadamantane (**1**) and 2.8 *g* (20 *mmol*) of benzoyl chloride. Yield 2.70 *g* (62*%*), R_f 0.80, mp. 218-219 *°C*. IR spectrum, ν, *cm*$^{-1}$: 1609 (C=Carom), 3057 (OH). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J, Hz*): 0.8 (3H, t, *J* = 7.6, CH_3CH_2); 0.92 (3H, s, CH_3CH_2); 1.2-1.4 (4H, s, 2 × CH_3); 2.76 (1H, br. d, *J* = 12.5, CH); 3.02 (2H, dt, *J* = 13.8, NCH_2); 3.21-3.38 (3H, m, NCH_2) and 3.61 (1H, NCH_2), 4.22 (1H) and 4.41 (1H, NCH_2); 4.90 (1H, d, *J* = 5.0, CH-OH); 7.40 (10H, s, 2×C_6H_5). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 6.44; 25.5; 36.7 16.2 (2×C_2H_5); 44.4; 48.2; 50.2; 54.2; 71.1; 126.6; 126.7; 127.5; 127.6; 128.2; 128.3; 136.2; 136.7; 169.1; 169.2. Found, *%*: C 73.84; H 7.33; N .6.84. $C_{25}H_{30}N_2O_3$. Calculated, *%*: C 73.89; H 7.37; N. 6.89.

1-Methyl-5-phenyl-9-oxo-3,7-di-(methylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**12**)**.** Prepared from 2.42 *g* (10 *mmol*) of 5-methyl-7-phenyl-6-oxo-1,3-diazaadamantane (**1**) and 1.57 *g* (20 *mmol*) of acetyl chloride. Yield 2.8 *g* (89*%*), R_f 0.41, mp. 138-139 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1606 (C=Carom), 1644.1722 (C=O). ^{1}H NMR spectrum, (300 *MHz*, $CDCl_3$) δ, ppm, (*J, Hz*): 1.02 (3H, s, CH_3); 3.22 (2H, br. d, *J* = 14.5, NCH_2); 3.57-3.62 (8H, m, 2×CH_3, NCH_2); 4.41 (2H, br.s, NCH_2); 4.82 (2H, br.s, NCH_2); 7.21-7.40 (5H, m, C_6H_5). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 16.3; 45.6; 52.3; 54.7; 55.1; 126.8; 127.1; 127.4; 135.9; 154.4; 208.4 (CO). Found, *%*: C 62.47; H 6.48; N 8.14. $C_{18}H_{22}N_2O_2$. Calculated, *%*: C 62.42; H 6.42; N 8.09.

1-Methyl-5-phenyl-9-oxo-3,7-di-(propylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**13**)**.** Obtained from 2.42 *g* (10 *mmol*) of 5-methyl-7-phenyl-6-oxo-1,3-diazaadamantane (**1**) and 2.13 *g* (20 *mmol*) of butyric acid

chloride. Yield 2.5 *g* (68%), R_f 0.61, mp. 108-110 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1610 (C=Carom), 1639, 1721 (C=O). ^{1}H NMR spectrum, (300 *MHz*, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.93 (3H, t, *J* = 7.4, CH_3CH_2); 0.96 (3H, t, *J* = 7.4, CH_3CH_2); 1.06 (3H, s, CH_3); 1.46-1.61 (4H, m, 2×CH_2CH_3); 2.17-2.32 (2H, m, $CH_2C_2H_5$); 2.36-2.48 (2H, m, $CH_2C_2H_5$); 2.91 (1H, dd, *J* = 13.5, 2.4); 3.29 (1H, dd, *J* = 13.5, 2.4); 3.35 (1H, dd, *J* = 13.3, 2.4); 3.79 (1H, dd, *J* = 13.3, 2.7), 4.25 (1H, dd, *J* = 13.3, 2.4), 4.37 (1H, dd, *J* = 13.3, 2.7), 5.02 (1H, dd, *J* = 13.5, 2.6); 5.37 (1H, dd, *J* = 13.3, 2.6, 4×CH_2); 7.26-7.40 (5H, m, C_6H_5). ^{13}C NMR spectrum (100 *MHz*, $CDCl_3$) δ, ppm: 13.45; 13.48; 16.41; 17.55; 33.99; 34.1; 45.3; 51.6; 51.9; 52.3; 55.8; 56.0; 126.8; 127.2(C); 127.4(C); 136.1; 170.6; 170.8; 208.5 (CO). Found, %: C 71.40; H 8.14; N 7.50. $C_{22}H_{30}N_2O_3$. Calculated,%: C 71.35; H 8.10; N 7.56.

1-Methyl-5-phenyl-9-oxo-3,7-di-(4'-methylbenzoyl)-3,7-diazabicyclo/3.3.1/nonane (**14**)**.** Prepared from 2.42 *g* (10 *mmol*) of 5-methyl-7-phenyl-6-oxo-1,3-diazaadamantane (**1**) and 3.08 *g* (20 *mmol*) of 4-methylbenzoyl chloride. Yield 3.0 *g* (66%), R_f 0.57, mp. 231-232 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1610 (C=Carom), 1639, 1721 (C=O). ^{1}H NMR spectrum, (300 MHz, CDCl3) δ, ppm, (*J*, *Hz*): 1.00 (3H, s, CH_3); 2.39 (3H, br.s, CH_3-arom); 2.42 (3H, br. s, CH_3-arom); 3.18 (1H, br. d, *J* = 12.6); 3.52–3.65 (2H, m), 3.93–4.09 (2H, m), 4.23 (1H, br. d, *J* = 11.6), 4.83 (1H, br. d, *J* = 13.2), and 5.15 (1H, br. e, *J* = 12.8, 4×CH_2); 7.18-7.35 (9H, m) and 7.38 - 7.44 (4H, m, H-arom). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 16.6 (CH_3), 20.8 (2×CH_3); 45.5; 52.2; 52.4 (br.s), 52.9 (br.s), 58.5 (br.s), 58.7 (br.s); 58.9 (br.s); 126.8(CH); 127.0 (2×CH); 127.4 (4×CH); 127.5 (2×CH); 128.2 (4×CH); 132.2; 135.8; 138.6; 169.4 (C CO), 208.5 (CO-adam.). Found, %: C 77.32; H 7.78; N 6.04. $C_{30}H_{30}N_2O_3$. Calculated, %: C 77.26; H 7.73; N 6.09.

1-Methyl-5-phenyl-9-oxo-3,7-di-(2'-furancarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**15**)**.** Prepared from 2.42 *g* (10 *mmol)* of 5-methyl-7-phenyl-6-oxo-1,3-diazaadamantane (1) and 2.61 *g* (20 *mmol*) of furan-2-carboxylic acid Cl-anhydride. Yield 2.5 *g* (60%), R_f 0.70, mp. 170-171 ^{o}C. IR spectrum, ν, cm^{-1}: 1565, 1610, 1629 (furyl); 1710 (C=O). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J*, *Hz*): 1.12 (3H, s, CH_3); 3.41 (2H, br s, CH_2); 3.75 (2H, br.s, CH_2); 4.81 (2H, br. s, CH_2); 5.10 (2H, br s, CH_2); 6.48 (2H, br. s, 2H-4fur); 6.91 (2H, br. d, J = 13.3, 2H-3fur); 7.28-7.42 (5H, m, C_6H_5); 7.52 (2H, br. s, 2H-5fur). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 16.5 (CH_3); 45.8(C); 52.5(C); 52.0-57.0 (br.s, 4×CH_2); 110.7 (2C-4truck); 116.2 (2C-3truck); 126.9 (C-4ph); 135.9 (C-ipso); 143.4 (2C-5truck); 147.1 (2C-2truck); 157.9 (2NCO); 208.1 (CO). Found, %: C 54.60; H 5.31; N. 6.73. $C_{24}H_{22}N_2O_5$. Calculated, %: C 54.54; H 5.26; N. 6.69.

1-Methyl-5-phenyl-9-oxo-3,7-di-(benzoyl)-3,7-diazabicyclo/3.3.1/nonane (**16**)**.** Obtained from 2.42 *g* (10 *mmol*) of 5-methyl-7-phenyl-6-oxo-

1,3-diazaadamantane (**1**) and 2.81 *g* (20 *mmol*) of benzoyl chloride. Yield 3.0 *g* (68.5%), R_f 0.45, mp. 228-229 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1619 (C=Carom), 1644, 1726 (C=O). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J, Hz*): 1.01 (3H, s, CH_3); 3.22 (1H, br.d, *J* = 13.7); 3.57–3.68 (2H, m), 4.02 (2H, br. d, *J* = 13.0), 4.21 (1H, br. d, *J* = 13.2); 4.87 (1H, br.d, *J* = 13.7) and 5.18 (1H, br. d, *J* = 13.5, 4×CH_2); 7.20-7.36 (5H, m), 7.37-7.50 (6H, m) and 7.51-7.59 (4H, m, 3ph). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 16.5 (CH3), 45.5 (C); 52.1(C); 52.4 (br.s, CH_2); 52.8 (br.s, CH_2); 58.4 (br.s, CH_2); 126.8(CH); 127.0 (2×CH); 127.3 (4×CH); 127.5 (2×CH); 127.6 (4H) 128.9 (2×CH); 135.2 (2× Cipso); 135.7 (Cipso); 169.3 (2×NCO), 208.4 (C=O). Found, %: C 76.7732; H 5.94; No. 6.44. $C_{28}H_{26}N_2O_3$. Calculated, %: C 76.71; H 5.90; N. 6.39.

1,5-Diphenyl-9-oxo-3,7-di-(ethylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**17**)**.** Prepared from 2.82 *g* (10 *mmol*) of 5,7-diphenyl-6-oxo-1,3-diazaadamantane (**1**) and 1.85 *g* (20 *mmol*) of propionic acid Cl anhydride. Yield 3.1 *g* (76%); R_f 0.80, m.p. 188-189 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1610 (C=Carom), 1639, 1720 (C=O). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J, Hz*): 1.2 (6H, s, 2 × CH_2CH_3); 2.1-3.8 (2H, m, CH_2); 1.51-2.65 (2H, m, CH_2); 3.52 (2H, br. d, *J* = 13.7, NCH_2); 4.08 (2H, br. d, *J* = 13.7, NCH_2); 4.51 (2H, br. d, *J* = 13.5, NCH_2); 5.42 (2H, br. d, *J* = 13.5, NCH_2); 7.26-7.42 (10H, m, 2×C_6H_5). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 8.6 ($2CH_3$); 25.4 (2×CH_2); 51.7 (2×NCH_2); 52.1 (3×NCH_2); 55.7 (2×NCH_2); 126.7 (2C); 127.3; 127.4; 136.3; 171.6; 206.5 (CO). Found, %: C 74.30; H 6.94; N. 6.88. $C_{25}H_{28}N_2O_3$. Calculated, %: C 74.25; H 6.90; N. 6.93.

1,5-Diphenyl-9-oxo-3,7-di-(furancarbonyl)-3,7-diazabicyclo/3.3.1/-nonane (**18**). Prepared from 2.82 *g* (10 *mmol*) of 5,7-diphenyl-6-oxo-1,3-diazaadamantane (**1**) and 2.61 *g* (20 *mmol*) of furancarboxylic acid Cl anhydride. Yield 3.12 *g* (63%), R_f 0.56, mp. 220-221 *°C*. IR spectrum, ν, cm^{-1}: 1571 (fur); 1613 (C=Carom), 1720, 1731 (C=O). ^{1}H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J, Hz*): 3.90 (2H, br. s), 4.15 (2H, br. s), and 5.19 (4H, br. s, 4 ×CH_2); 6.49 (2H, dd, *J* = 3.3, 1.6, 2H-4fur); 6.95 (2H, br. d, *J* = 3.3, 1.6, 2H-3fur); 7.29-7.45 (10H, 2ph). 7.52 (2H, br. s, 5 trucks). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 52.7 ($4CH_2$); 66.1 (2×C); 110.7 (2×C-4-truck); 116.4 (2×C-3-truck); 126.9 (2CH, ph); 127.3 (4CH, ph); 127.5 (4CH, ph); 136.2; 143.5 (2×C-3-truck); 147.1; 158.0; 206.1 (CO). Found,%: C 52.55; H 5.06; N 5.77. $C_{29}H_{24}N_2O_5$. Calculated,%: C 52.50; H 5.01; N 5.83.

1,5-Diphenyl-9-hydroxy-3,7-di-(methylcarbonyl)-3,7-diazabicyclo/3.3.1/nonane (**19**). Prepared from 2.82 *g* (10 *mmol*) of 5,7-diphenyl-6-hydroxy-1,3-diazaadamantane (**1**) and 1.57 *g* (20 *mmol*) of acetic acid chloride. Yield 2.4 *g* (64%), R_f 0.45, m.p. 255-256 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1606 (C=Carom), 1640 (N-C=O); 3326 (OH). ^{1}H NMR spectrum, (300

MHz, $CDCl_3$) δ, ppm, (*J*, *Hz*): 1.96 (3H, s, CH_3); 2.18 (3H, s, CH_3); 2.86 (2H, br. d, *J* = 13.5, NCH_2); 3.32 (1H, br. d, *J* = 12.5, NCH_2); 3.48 (1H, br. d, NCH_2); 3.81 (2H, br. d, *J* = 13.5, NCH_2); 4.18 (1H, br. d, *J* = 12.5, CHOH); 4.78 (2H, br. d, *J* = 12.5, NCH_2); 5.15 (1H, d, *J* = 7.1, CHOH); 7.21-7.65 (10H, m, 2×C_6H_5). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 20.8; 21.4; 40.1; 41.3; 41.4; 42.0; 47.4; 51.2; 56.6; 71.01; 125.9 (2CH, ph); 126.02 (2CH, ph); 126.13 (2CH, ph); 127.9 (2CH, ph); 128.0 (2CH, ph); 141.3; 141.4; 167.7; 168.7. Found, *%*: C 74.96; H 5.90; N 7.49. $C_{23}H_{26}N_2O_3$. Calculated, *%*: From 75.00; H 5.85; N 7.44.

1,5-Diphenyl-9-hydroxy-3,7-di-(cyclopropanolcarbonyl)-3,7-diaza-bicyclo-/3.3.1/nonane (**20**). Prepared from 2.4 *g* (10 *mmol*) of 5,7-diphenyl-6-hydroxy-1,3-diazaadamantane (**1**) and 1.57 *g* (20 *mmol*) of acetic acid chloride. Yield 2.4 *g* (56%), R_f 0.68, mp. 218-220 *°C*. IR spectrum, *ν, cm*$^{-1}$: 1606 (C=Carom), 1640 (C=O); 3326 (OH). ^1H NMR spectrum, (300 MHz, $CDCl_3$) δ, ppm, (*J*, *Hz*): 0.51-1.02 (8H, m, 4×CH_2); 0.71 (1H, br. d, *J* = 13.5, CH); 1.90 (1H, br. d, *J* = 13.9, CH); 2.88 (2H, br. d, *J* = 13.5, NCH_2); 3.4 (2H, t, *J* = 6.8, NCH_2); 3.84 (1H, br. d, *J* = 12.9, CHOH); 4.16 (1H, br. d, *J* = 12.9, CHOH); 4.56 - 4.96 (4H, m, 2 × NCH_2); 7.21-7.45 (6H, m, H-arom); 7.62 (4H, br. d, *J* = 13.9, H-arom). ^{13}C NMR spectrum (100 MHz, $CDCl_3$) δ, ppm: 6.57 (CH_2); 6.8 (CH_2-pr); 10.4 (CH_2-pr); 11.0 (CH_2-pr); 43.2 (NCH_2); 46.1 (NCH_2); 52.3 (NCH_2); 55.8 (NCH_2); 7.03 (C-OH); 125.9 (2CH, ph); 126.1 (5CH, ph); 127.9 (5CH, ph); 170.3 (2N-CO); 171.3(2C). Found, *%*: C 75.39; H 5.02; No. 6.46. $C_{27}H_{30}N_2O_3$. Calculated, *%*: C 75.34; H 6.97; N. 6.51.

СИНТЕЗ И ПРОТИВОСУДОРОЖНАЯ АКТИВНОСТЬ НОВЫХ ПРОИЗВОДНЫХ 1,3-ДИАЗААДАМАНТАНОВ

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Работа посвещена синтезу и изучению нейротропной активности некоторых производных 3,7-диазабицикло/3.3.1/нонанов. Для этого были синтезированы различные 5,7-диалкил, метилфенил-, дифенил-1,3-диазаадамантаны **1**, которые при взаимодействии с Cl-ангидридами алифатических, ароматических, карбоциклических и гетероциклических кислот превращены в соответсвующие 3,7-диазабицикло/3,3,1/нонаны. Изучена противосудорожная активность синтезированных соединений, среди них выявлены вещества с выраженной антикоразоловой активностью.

На основе данных биологических исследованиях можно предположить, что на антикоразоловую активность вероятно больше влияной заместители в 1-ом и 5-ом положениях бициклононанов, чем остаток соответствующий кислоты.

1,3-ԴԻԱԶԱԱԴԱՄԱՆՏԱՆՆԵՐԻ ԱԾԱՆՑՅԱԼՆԵՐԻ ՍԻՆԹԵԶԸ ԵՎ ՆՐԱՆՑ ՀԱԿԱՑՆՑՈՒՄԱՑԻՆ ԱԿՏԻՎՈՒԹՅԱՆ ՈՒՍՈՒՄՆԱՍԻՐՈՒԹՅՈՒՆԸ

Ա.Դ. ՀԱՐՈՒԹՅՈՒՆՑԱՆ, Ք. Ա. ԳԵՎՈՐԳՑԱՆ, Մ. Վ. ԳԱԼՍՏՑԱՆ, Ռ. Գ. ՊԱՐՈՆԻԿՑԱՆ, Ի. Ե. ՆԱԶԱՐՑԱՆ

Սինթեզվել են 5,7-դիրքերում տարբեր ալկիլ, ալկիլֆենիլ, դիֆենիլ խմբեր պարունակող 1,3-դիազաադամանտաններ: Վերջիններիս փոխազդեցությունը տարբեր ալիֆատիկ, արոմատիկ, կարբոցիկլիկ, հետերոցիկլիկ թթուների քլո- րանհիդրիդների հետ հանգեցրել է համապատասխան 3,7-դիազաբիցիկլոնոնան- ների առացման: Ուսումնասիրվել են սինթեզված միացությունների հակակո- րազոլային հատ- կությունները, որոշ միացություններ ցուցաբերել են արտա- հայտված կորա- զոլային ակտիվություն:

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