ISSN 1070-4280, Russian Journal of Organic Chemistry, 2019, Vol. 55, No. 3, pp. 368–372. © Pleiades Publishing, Ltd., 2019.
Russian Text © The Author(s), 2019, published in Zhurnal Organicheskoi Khimii, 2019, Vol. 55, No. 3, pp. 427–432.

Synthesis of 1-Butyl-3,6-diazahomoadamantane

R. T. Alasadi[a], A. H. A. Al-Yasari[a], H. F. Abdulhasan[a], V. V. Kalashnikov[b], and T. M. Serova[b]*

[a] *University of Kerbala, P.O. Box 1125, Kerbala, Iraq*

[b] *Institute of Physiologically Active Compounds, Russian Academy of Sciences, Severnyi proezd 1, Chernogolovka, Moscow oblast, 142432 Russia*
**e-mail: tetraza@mail.ru*

Received June 14, 2018; revised June 25, 2018; accepted September 11, 2018

Abstract—1-Butyl-3,6-diazahomoadamantan-9-one was synthesized by condensation of heptan-2-one with diethylenetetramethylenetetramine (1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane). Reactions of the title compound at the carbonyl group afforded 1-butyl-3,6-diazahomoadamantane and derivatives containing functional groups on the C^9 bridging atom. Introduction of pharmacophoric groups into the 9-position of 1-butyl-3,6-diazahomoadamantane seems to be the most promising method for its modification with a view to obtaining derivatives with new biological properties.

Keywords: condensation, heptan-2-one, [1^4.2^2]adamanzane, 1-butyl-3,6-diazahomoadamantan-9-one, 1-butyl-3,6-diazahomoadamantane and its derivatives.

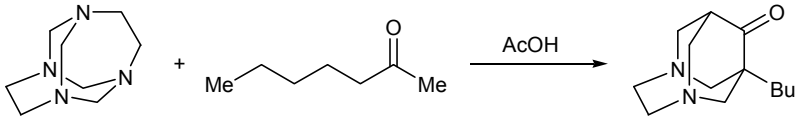
DOI: 10.1134/S1070428019030163

We previously described the synthesis of a number of 1-substituted 3,6-diazahomoadamantan-9-ones by condensation of ketones with diethylenetetramethylenetetramine ([1^4.2^2]adamanzane, 1,3,6,8-tetraazatricyclo[4.4.1.1^{3,8}]dodecane) and their further transformations to 3,6-diazahomoadamantane and its derivatives [1, 2]. It is known that heptan-2-one is an alarm pheromone of bees; it shows analgesic and pronounced anesthetic properties and therefore can be used to obtain local anesthetics [3–7]. In continuation of our studies on the synthesis of new 3,6-diazahomoadamantane derivatives, by condensation of heptan-2-one with diethylenetetramethylenetetramine we obtained 1-butyl-3,6-diazahomoadamantan-9-one (**1**) which retained the initial heptane-2-one smell. It was anticipated that compound **1** would possess both pheromone and analgesic and anesthetic properties.

The reaction of diethylenetetramethylenetetramine with heptan-2-one was carried out in isopropyl alcohol at room temperature (Scheme 1). Compound **1** was also synthesized starting from ethylenediamine and paraformaldehyde in a one-pot fashion without isolation of diethylenetetramethylenetetramine. The IR spectrum of **1** displayed a carbonyl stretching band at 1711 cm^{-1}. Its ^{1}H NMR spectrum contained a set of signals typical of diazahomoadamantane skeleton, namely two *AB* systems due to NCH_2C protons, a multiplet of the NCH_2CH_2N ethylene bridge, and a singlet at δ 2.53 ppm due to proton in the bridgehead position. The butyl group gave rise to a triplet at δ 0.88 ppm (CH_3) and multiplets in the region δ 1.14–1.37 ppm (6H, CH_2). In the mass spectrum of **1** we observed the molecular ion peak with *m*/*z* 222 $[M]^+$ whose main decomposition pathway involved cleavage of the cage skeleton with the formation of ions with *m*/*z* 72 and 58.

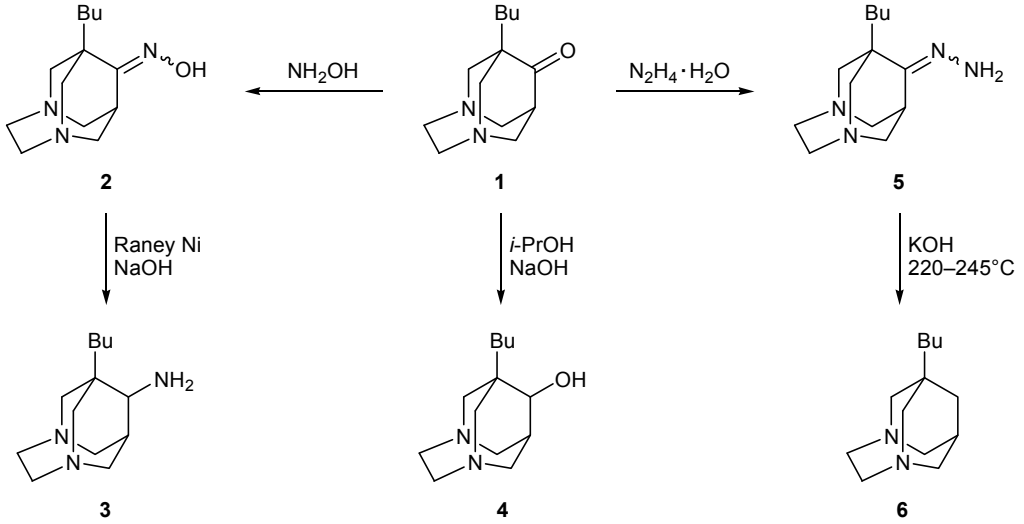
Diazahomoadamantanone **1** is a promising intermediate product for the preparation of new diazahomo-

Scheme 1.



1

Scheme 2.



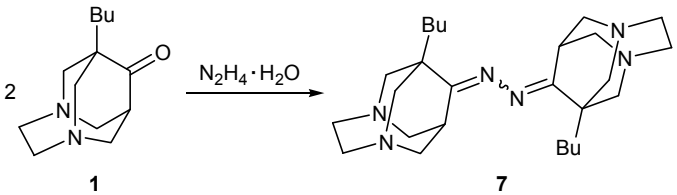
adamantane derivatives via functionalization at the carbonyl group (Scheme 2). Treatment of **1** with hydroxylamine gave oxime **2** which was reduced to amine **3** over Raney nickel an aqueous alkali. The IR spectrum of **2** showed absorption bands at 1620 and 3240 cm^{-1} due to stretching vibrations of C=N bond and OH group, respectively. The fragmentation of **2** under electron impact was characterized by elimination of OH radical from the molecular ion to give $[M - 17]^+$ ion.

Ketone **1** was reduced to odorless alcohol **4** which displayed OH stretching band in the IR spectrum at 3290–3430 cm^{-1}. The reaction of **1** with hydrazine hydrate followed different paths, depending on the temperature. The corresponding hydrazone **5** was formed at a temperature below 50°C, whereas azine **7** was obtained when a mixture of ketone **1** and 80% hydrazine hydrate was heated under reflux (Scheme 3). Treatment of hydrazone **5** with excess potassium hydroxide at 220–245°C afforded 1-butyl-3,6-diazahomoadamantane (**6**). In the ^1H NMR spectrum of **6**, methylene protons of the C^9H_2 group resonated as a singlet at δ 1.60 ppm, the singlet at δ 1.82 ppm was assigned to CH proton in the bridgehead position (C^8), four NCH_2C groups gave doublets at δ 2.11, 2.25, 2.63, and 3.25 ppm, and the signal of the NCH_2CH_2N protons was a multiplet at δ 3.05 ppm. The butyl substituent was represented by a triplet at δ 0.89 ppm (Me) and multiplets in the region δ 1.01–1.40 ppm (6H, CH_2).

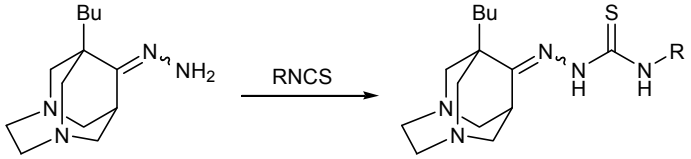
In the IR spectrum of **7** we observed C=N stretching band at 1635 cm^{-1}, whereas no bands assignable to NH_2 group were present. Each of the C=N bonds in molecule **7** may have *cis* or *trans* configuration, so that the formation of isomer mixture is possible. In our case, both C=N bonds are configured *trans*, which is confirmed by the ^1H NMR spectrum where only one 8-H signal was observed at δ 2.53 ppm [8]. The mass spectrum of **7** contained the molecular ion peak with *m*/*z* 440 $[M]^+$ and $[M/2]^+$ peak with *m*/*z* 220. The main fragmentation path of the molecular ion is decomposition of the cage skeleton with the formation of $CH_2=N^+CH_2$, $CH_2=N^+(CH_3)_2$, and $CH_3CH=N^+(CH_3)_2$ ions with *m*/*z* 42, 58, and 72, respectively.

It is known that thiosemicarbazones are promising compounds from the viewpoint of searching for new chemotherapeutic agents [9–11]. Introduction of a pharmacophoric group into the 9-position of butyldiazahomoadamantane seemed to be the most appropriate method of its modification with the goal of obtaining compounds possessing new biological properties. For this purpose, hydrazone **5** was reacted

Scheme 3.



Scheme 4.



8, R = Me; **9**, R = Ph; **10**, R = $MeO(CH_2)_2$.

with methyl, phenyl, and 2-methoxyethyl isothiocyanates. As a result, we isolated *N*-substituted thiosemicarbazones **8**–**10** (Scheme 4) whose structure was confirmed by spectral data.

Fragmentation of molecular ions of 3,6-diazahomoadamantane derivatives is characterized by formation of ions both common for these compounds and those resulting from decomposition of the functional substituent. The molecular ion of **5** decomposed via cleavage of the N–N bond to peoduce $[M - NH_2]^+$ and $[M - NAd]^+$ ions, followed by elimination of nitrogen-containing molecules $C_nH_{2n+1}N$ (n = 1–3). The mass spectra of thiosemicarbazones **8**–**10** characteristically displayed elimination of the NHC(S)NHR substituent from the molecular ion.

Thus, we have synthesized previously unknown 3,6-diazahomoadamantane derivatives which attract interest as potential biologically active compounds.

EXPERIMENTAL

The IR spectra were recorded in KBr on a Bruker IFS spectrometer. The ^1H and ^{13}C NMR spectra were recorded from solutions in $CDCl_3$ on a Bruker AM-300 spectrometer at 300.13 and 75.47 MHz, respectively, using TMS as internal standard. The mass spectra (electron impact, 70 eV) were obtained on a Kratos MS-30 instrument with direct sample admission into the ion source (ion source temperature 200°C).

1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-one (1). *a*. A mixture of 8.40 g (50 mmol) of diethylenetetramethylenetetramine, 6.30 g (55 mmol) of heptan-2-one, and 9.00 g (150 mmol) of acetic acid in 50 mL of isopropyl alcohol was stirred for 72 h at room temperature. The mixture was then concentrated under reduced pressure, the viscous residue was extracted with hot *n*-heptane (4×40 mL), and the warm extract was passed through a layer of anhydrous alumina (10 g, Brockmann activity II) on a Schott filter. The solvent was distilled off, and the residue was recrystallized from *n*-heptane.

b. Paraformaldehyde, 6.00 g (200 mmol), was added to a solution of 6.00 g (100 mmol) of ethylenediamine in 50 mL of isopropyl alcohol, and the mixture was stirred until it became homogeneous. Heptan-2-one, 6.30 g (55 mmol), and acetic acid, 9.00 g (150 mmol), were added to the resulting solution, and the mixture was stirred for 72 h at room temperature. The product was isolated and purified as described above in *a*. Yield 3.90 g (35%) (*a*), 3.65 g (33%) (*b*); white crystals, mp 65–67°C (from *n*-heptane). IR spectrum: ν 1711 cm^{-1} (C=O). ^1H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, J = 7.4 Hz), 1.14–1.32 m (4H, CH_2), 1.37 m (2H, CH_2), 2.53 s (1H, CH), 3.04 m (4H, NCH_2CH_2N), 3.09–3.24 m (6H, NCH_2C), 3.39 d (2H, NCH_2C, J = 13.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 212.10 (C^9), 61.30 (C^2, C^{10}), 59.15 (C^4, C^5), 57.30 (C^7, C^{11}), 51.10 (C^8), 44.95 (C^1), 33.10 (1-CH_2), 27.25 (1-CH_2**C**H_2), 23.15 (**C**H_2Me), 15.05 (Me). Mass spectrum, m/z (I_{rel}, %): 222 (100) $[M]^+$, 164 (73), 150 (30), 137 (19), 131 (21), 122 (20), 101 (50), 72 (35), 58 (60) 57 (40), 43 (41). Found, %: C 70.12; H 10.11; N 12.49. $C_{13}H_{22}N_2O$. Calculated, %: C 70.23; H 9.97; N 12.60. M 222.33.

1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-one oxime (2). Hydroxylamine hydrochloride, 0.42 g (6 mmol), was added to a solution of 1.10 g (5 mmol) of compound **1** in 5 mL of water. The mixture was heated to 60–70°C, and a solution of 0.62 g (6 mmol) of sodium carbonate in 5 mL of water was added in portions over a period of 15 min with continuous stirring. The mixture was stirred for 10 min more at that temperature, and the precipitate was filtered off, dried, and recrystallized from toluene. Yield 0.85 g (73%), white crystals, mp 157–158°C. IR spectrum, ν, cm^{-1}: 3240 (OH), 1620 (C=N). ^1H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, J = 7.4 Hz), 1.15–1.33 m (4H, CH_2), 1.37 m (2H, CH_2), 2.53 s (1H, CH), 3.04 m (4H, NCH_2CH_2N), 3.09–3.24 m (6H, NCH_2C), 3.39 d (2H, NCH_2C, J = 14.0 Hz), 8.60 s (1H, OH). Mass spectrum, m/z (I_{rel}, %): 237 (100) $[M]^+$, 220 (100), 194 (09), 177 (40), 163 (05), 121 (10), 72 (20), 58 (37), 43

(10), 42 (50). Found, %: C 65.85; H 9.73; N 17.63. $C_{13}H_{23}N_3O$. Calculated, %: C 65.79; H 9.77; N 17.70. *M* 237.34.

1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-amine (3). A solution of 1.84 g of sodium hydroxide in 15 mL of water was added dropwise with vigorous stirring over a period of 1 h to a suspension of 0.50 g (2.10 mmol) of oxime **2** and 1.84 g of Raney nickel (Ni–Al, 50:50) in 10 mL of water at such a rate that the temperature of the mixture did not exceed 50°C. The mixture was then stirred for 2 h more, cooled, and filtered, and the filtrate was extracted with diethyl ether (3×10 mL). The extract was dried over potassium hydroxide and evaporated. Yield 0.36 g (77 %), white crystals, mp 86–88°C. IR spectrum, ν, cm^{-1}: 3395, 3246 (NH_2). ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, CH_3, *J* = 6.9 Hz), 1.16–1.38 m (4H, CH_2), 1.42 m (2H, CH_2), 1.62 s (2H, NH_2), 1.79 br.s (1H, CH); 2.30 d, 2.45 d, and 2.58 d (2H each, NCH_2C, *J* = 14.0 Hz); 3.04 m (4H, NCH_2CH_2N), 3.32 d (1H, C**H**NH_2, *J* = 11.0 Hz), 3.49 d (2H, NCH_2C, *J* = 14.0 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 223 (100) $[M]^+$, 181 (14), 165 (23), 150 (35), 138 (36), 98 (25), 83 (30), 72 (60), 58 (50), 57 (27), 42 (71). Found, %: C 69.75; H 11.37; N 18.65. $C_{13}H_{25}N_3$. Calculated, %: C 69.91; H 11.28; N 18.81. *M* 223.36.

1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-ol (4). A mixture of 0.50 g (2.25 mmol) of ketone **1** and 0.06 g (2.50 mmol) of anhydrous sodium hydroxide in 10 mL of isopropyl alcohol was refluxed for 3.5 h. The solvent was distilled off, and the dry residue was extracted with toluene (2×10 mL), the extract was evaporated, and the residue was recrystallized from toluene. Yield 0.39 g (78%), white crystals, mp 124–125°C. IR spectrum, ν, cm^{-1}: 3430, 3297 (OH). ^{1}H NMR spectrum, δ, ppm: 0.88 t (3H, CH_3, *J* = 7.4 Hz), 1.14–1.32 m (4H, CH_2), 1.37 m (2H, CH_2), 2.53 s (1H, CH), 3.04 m (4H, NCH_2CH_2N), 3.10–3.28 m (6H, NCH_2C), 3.38 d (2H, NCH_2C, *J* = 13.9 Hz), 3.45 s (1H, C**H**OH), 3.58 s (1H, OH). Mass spectrum, *m*/*z* (I_{rel}, %): 224 (95) $[M]^+$, 207 (12), 181 (30), 167 (33), 166 (35), 152 (27), 111 (40), 72 (65), 58 (100), 42 (85). Found, %: C 69.45; H 10.89; N 12.31. $C_{13}H_{24}N_2O$. Calculated, %: C 69.60; H 10.78; N 12.49. *M* 224.34.

(1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-ylidene)hydrazine (5). A solution of 1.10 g (5 mmol) of ketone **1** in 10 mL of 80% hydrazine hydrate was heated for 3 h at a temperature not exceeding 50°C. The mixture was evaporated, and the residue was recrystallized from toluene. Yield 1.0 g (85%), white crystals, mp 125–126°C. IR spectrum, ν, cm^{-1}: 1630 (C=N), 3270, 3360 (NH). ^{1}H NMR spectrum, δ, ppm: 0.85 t (3H, CH_3, *J* = 7.4 Hz), 1.18–1.35 m (4H, CH_2), 1.40 m (2H, CH_2), 2.50 s (1H, CH), 3.02 m (4H, NCH_2CH_2N), 3.10–3.26 m (6H, NCH_2C), 3.38 d (2H, NCH_2C, *J* = 13.9 Hz), 5.17 br.s (2H, NH_2). Mass spectrum, *m*/*z* (I_{rel}, %): 236 (100) $[M]^+$, 200 (25), 207 (10), 194 (14), 178 (13), 164 (09), 121 (16), 72 (95), 58 (36), 42 (45). Found, %: C 66.20; H 10.35; N 23.50. $C_{13}H_{24}N_4$. Calculated, %: C 66.06; H 10.23; N 23.70. *M* 236.36.

1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecane (6). Hydrazone **5**, 0.60 g (2.5 mmol), was thoroughly mixed with 0.6 g (11 mmol) of potassium hydroxide, and the mixture was heated for 2 h at 220–240°C. The mixture was cooled and extracted with toluene (3×20 mL), the solvent was distilled off from the extract, and the residue was recrystallized from toluene. Yield 0.25 g (47%), white crystals, mp 39–40°C (from toluene). ^{1}H NMR spectrum, δ, ppm: 0.89 t (3H, CH_3, *J* = 6.90 Hz), 1.01–1.22 m (4H, CH_2), 1.40 m (2H, CH_2), 1.60 s (2H, CH_2), 1.82 s (1H, CH); 2.11 d, 2.25 d, and 2.63 d (2H each, NCH_2C, *J* = 14.0 Hz); 3.05 m (4H, NCH_2CH_2N), 325 d (2H, NCH_2C, *J* = 14.0 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 208 (60) $[M]^+$, 193 (11), 150 (32), 124 (42), 112 (22), 108 (42), 83 (20), 72 (100), 58 (23), 57 (44), 43 (71), 42 (50). Found, %: C 74.75; H 11.47; N 13.32. $C_{13}H_{24}N_2$. Calculated, %: C 74.94; H 11.61; N 13.45. *M* 208.34.

1,2-Bis(1-butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-ylidene)hydrazine (7). A solution of 1.10 g (5 mmol) of ketone **1** in 5 mL of 80% hydrazine hydrate was refluxed for 3 h. The mixture was evaporated, and the residue was recrystallized from toluene. Yield 0.95 g (87%), white crystals, mp 177–179°C. IR spectrum: ν 1635 cm^{-1} (C=N). ^{1}H NMR spectrum, δ, ppm: 0.85 t (6H, CH_3, *J* = 7.4 Hz), 1.18–1.35 m (8H, CH_2), 1.40 m (4H, CH_2), 2.53 s (2H, CH), 3.01 m (8H, NCH_2CH_2N), 3.10–3.26 m (12H, NCH_2C), 3.38 d (4H, NCH_2C, *J* = 13.9 Hz). Mass spectrum, *m*/*z* (I_{rel}, %): 440 (25) $[M]^+$, 397 (4), 356 (6), 282 (7), 220 (47), 177 (10), 150 (05), 72 (100), 58 (20), 42 (19). Found, %: C 70.97; H 10.17; N 18.95. $C_{26}H_{44}N_6$. Calculated, %: C 70.86; H 10.06; N 19.07. *M* 439.99.

1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-one thiosemicarbazones 8–10 (*general procedure***).** A mixture of 4 mmol of hydrazone **5** and 4 mmol of the corresponding isothiocyanate in 15 mL of toluene was refluxed for 2 h. The mixture was cooled, and the

precipitate was filtered off and recrystallized from isopropyl alcohol.

2-(1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-ylidene)-*N*-methylhydrazine-1-carbothioamide (8). Yield 1.10 g (84%), white crystals, mp 136–137°C. IR spectrum, ν, cm^{-1}: 3385, 3310 (NH), 1632 (C=N), 1577 (NCSN). Mass spectrum, *m*/*z* (I_{rel}, %): 309 (38) $[M]^+$, 278 (15), 220 (21), 191 (30), 167 (25), 157 (27), 119 (46), 72 (60), 58 (90), 43 (75). Found, %: C 58.14; H 8.68; N 22.81. $C_{15}H_{27}N_5S$. Calculated, %: C 58.21; H 8.79; N 22.63. *M* 309.47.

2-(1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-ylidene)-*N*-phenylhydrazine-1-carbothioamide (9). Yield 1.20 g (76%), white crystals, mp 161–162°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 3400, 3330 (NH), 1625 (C=N), 1599 (C=C_{arom}), 1558 (NCSN). Mass spectrum, *m*/*z* (I_{rel}, %): 371 (11) $[M]^+$, 279 (47), 220 (80), 175 (23), 160 (21), 152 (27), 105 (33), 72 (50), 58 (80), 42 (70). Found, %: C 64.19; H 7.78; N 19.09. $C_{20}H_{29}N_5S$. Calculated, %: C 64.65; H 7.87; N 18.85. *M* 371.54.

2-(1-Butyl-3,6-diazatricyclo[4.3.1.1^{3,8}]undecan-9-ylidene)-*N*-(2-methoxyethyl)hydrazine-1-carbothioamide (10). Yield 1.00 g (67%), white crystals, mp 125–126°C (from *i*-PrOH). IR spectrum, ν, cm^{-1}: 3385, 3310 (NH), 1632 (C=N), 1577 (NCSN), 1259, 1128 (OCH_3). Mass spectrum, *m*/*z* (I_{rel}, %): 353 (38) $[M]^+$, 279 (30), 220 (21), 191 (30), 167 (25), 157 (27), 119 (46), 72 (60), 58 (90), 43 (75). Found, %: C 57.23; H 8.69; N 19.74. $C_{17}H_{31}N_5S$. Calculated, %: C 57.76; H 8.84; N 19.81. *M* 353.53.

CONFLICT OF INTERESTS

No conflict of interests is declared by the authors.

REFERENCES

1. Razenko, I.O., Serova, T.M., and Kuznetsov, A.I., *Russ. Chem. Bull., Int. Ed*., 2016, vol. 65, p. 2458. doi 10.1007/s11172-016-1606-6
2. Kuznetsov, A.I., Alasadi, R.T., Senan, I.M., and Serova, T.M., *Russ. Chem. Bull., Int. Ed*., 2015, vol. 64, p. 962. doi 10.1007/s11172-015-0964-9
3. Vallet, A., Cassier, P., and Lensky, Y., *J. Insect Physiol*., 1991, vol. 37, p. 789. doi 10.1016/0022-1910(91)90076-C
4. Albro, P.W., Corbett, J.T., and Schroeder, J.L., *Chem.-Biol. Interact*., 1984, vol. 51, p. 295. doi 10.1016/0009-2797(84)90155-8
5. Barber, E.D., Miller, K.R., Banton, M.I., and Reddy, M.V., *Mutat. Res*., 1999, vol. 442, p. 133. doi 10.1016/S1383-5718(99)00072-8
6. Prokopy, R.J., Hu, Xi., Jang, E.B., Vargas, R.I., and Warthen, J.D., *J. Chem. Ecol*., 1998, vol. 24, p. 1293. doi 10.1023/A:1021218531083
7. Gutiérrez-García, A.G., Contreras, C.M., Mendoza-López, M.R., García-Barradas, O., and Cruz-Sánchez, J.S., *Physiol. Behav*., 2007, vol. 91, p. 166. doi 10.1016/j.physbeh.2007.02.006
8. Morgenstern, K., *Prog. Surf. Sci*., 2011, vol. 86, p. 115. doi 10.1016/j.progsurf.2011.05.0020
9. Zhu, T.-H., Cao, S.-W., and Yu, Y.-Y., *Int. J. Biol. Macromol*., 2013, vol. 62, p. 589. doi 10.1016/j.ijbiomac.2013.09.056
10. Pelosi, G., Bisceglie, F., Bignami, F., Ronzi, P., Schiavone, P., Re, M.C., Casoli, G., and Pilotti, E., *J. Med. Chem*., 2010, vol. 53, p. 8765. doi 10.1021/jm1007616
11. Jallapally, A., Addla, D., Yogeeswari, P., Sriram, D., and Kantevari, S., *Bioorg. Med. Chem. Lett*., 2014, vol. 24, p. 5520. doi 10.1016/j.bmcl.2014.09.084