ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 7, pp. 1083–1086. © Pleiades Publishing, Ltd., 2013.
Original Russian Text © A.A. Aghekyan, G.A. Panosyan, E.A. Markaryan, 2013, published in Zhurnal Organicheskoi Khimii, 2013, Vol. 49, No. 7, pp. 1097–1100.

SHORT COMMUNICATIONS

Synthesis of *N*′-Substituted *N*-(1-Phenylcyclopentylmethyl)oxamides

A. A. Aghekyan, G. A. Panosyan, and E. A. Markaryan

Research Technological Center of Organic and Pharmaceutical Chemistry, National Academy of Sciences of Armenia, Mndzhoyan Institute of Fine Organic Chemistry, pr. Azatutyan 26, Yerevan, 0014 Armenia
e-mail: aaghekyan@mail.ru

Received August 25, 2012

DOI: 10.1134/S1070428013070221

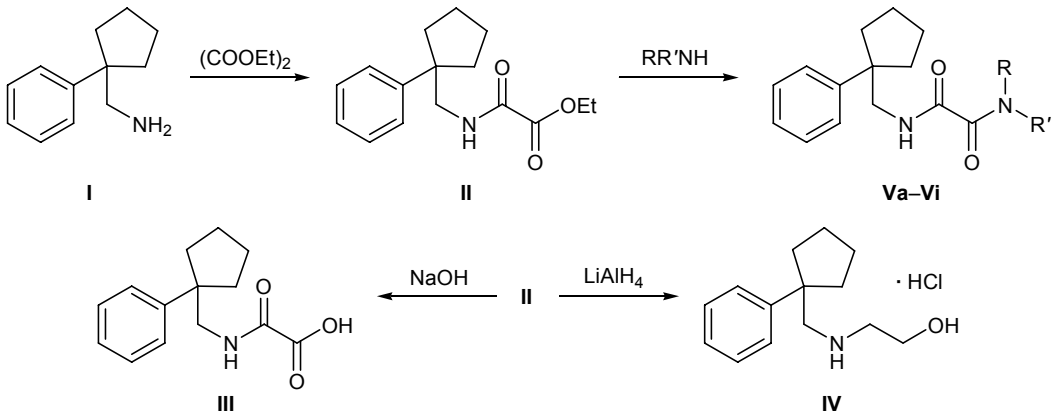
Some compounds containing a 1-phenylcyclopentylmethylamino group were found to exhibit a broad spectrum of biological activity [1]. In continuation of these studies we have synthesized new derivatives of (1-phenylcyclopentyl)methanamine (**I**) [2]. The latter reacted with 5 equiv of diethyl oxalate [3] to give amido ester **II** in 70–75% yield (Scheme 1). Alkaline hydrolysis of **II** afforded amido acid **III**, whereas the reduction of **II** with $LiAlH_4$ led to the corresponding amino alcohol which was characterized as hydrochloride **IV**.

We also examined reactions of **II** with various amines and found that, depending on the amine nature (alkyl-, hydroxyalkyl-, hetaryl-, and hetarylalkylamines), *N*-(1-phenylcyclopentylmethyl)-substituted oxamides are formed according to different schemes. The reactions of **II** with amines gave unsymmetrical oxamides **Va**–**Vh** in 60–70% yield (Scheme 1). Symmetric oxamide **Vi** was synthesized according to a similar scheme; it was also formed via condensation of amine **I** with an equimolar amount of diethyl oxalate. Depending on the amine nature, the condensations were carried out either in alcohol as solvent or by fusion of the initial reactants.

We failed to synthesize *N*,*N*′-disubstituted oxamides by reaction of amido ester **II** with substituted anilines; therefore, the target diamides **VIII** were obtained as shown in Scheme 2. The condensation of anilines **VIa**–**VIe** with diethyl oxalate gave N-phenyl amido esters **VIIa**–**VIIe**, and the latter reacted with amine **I** to produce oxamides **VIIIa**–**VIIIe**. All compounds synthesized in the present work were isolated as colorless crystalline substances. Their structure and purity were confirmed by spectral data and TLC.

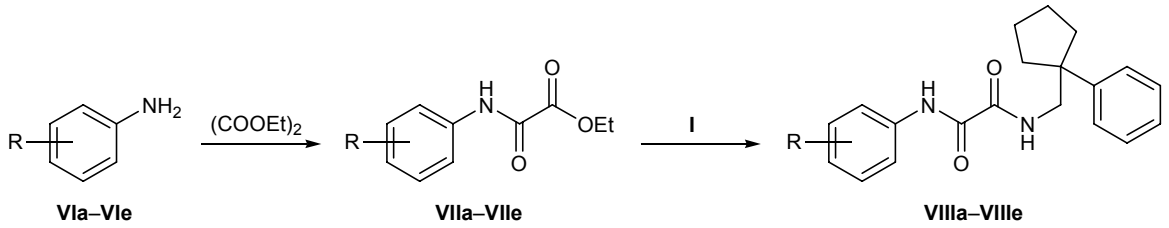
Ethyl 2-oxo-2-[(1-phenylcyclopentylmethyl)-amino]acetate (II). A solution of 17.5 g (0.1 mol) of

Scheme 1.



R = H, R′ = Bu (**a**); RR′N = pyrrolidin-1-yl (**b**), morpholin-4-yl (**c**); R = H, R′ = 1,3,4-thiadiazol-2-yl (**d**), pyridin-4-yl (**e**), $HOCH_2CH_2$ (**f**), 3-(morpholin-4-yl)propyl (**g**), furfuryl (**h**), 1-phenylcyclopentylmethyl (**i**).

Scheme 2.



R = 3-Br (**a**), 4-Br (**b**), 4-F (**c**), 3-F_3C (**d**), 2-MeO (**e**).

amine **I** in 100 ml of chloroform was slowly added dropwise to a boiling solution of 73 g (0.5 mol) of diethyl oxalate in 200 ml of chloroform. The mixture was heated for 10 h under reflux and evaporated, and the residue was distilled under reduced pressure. Yield 20 g (73%), bp 195–198°C (1 mm), mp 48–49°C (from hexane), R_f 0.63 (benzene–acetone, 8:1). IR spectrum, ν, cm^{-1}: 3317 (NH), 1744 (C=O, ester), 1683 (C=O, amide). Found, %: C 69.62; H 7.58; N 5.21. $C_{16}H_{21}NO_3$. Calculated, %: C 69.79; H 7.69; N 5.09.

2-Oxo-2-[(1-phenylcyclopentylmethyl)amino]-acetic acid (III). A mixture of 2 g (7.2 mmol) of amido ester **II** and 20 ml of 20% aqueous sodium hydroxide was stirred for 5 h at 35–40°C. The resulting transparent solution was acidified, and the precipitate was filtered off. Yield 1.5 g (83%), mp 98–100°C (from benzene), R_f 0.52 (benzene–acetone, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.63–2.03 m (8H, CH_2), 3.35 d (2H, NHC**H**$_2$, J = 6.5 Hz), 7.17 m (1H) and 7.24–7.31 m (4H (H_{arom}), 7.51 t (1H, NH, J = 6.5 Hz), 12.41 br.s (1H, OH). Found, %: C 68.17; H 6.83; N 5.74. $C_{14}H_{17}NO_3$. Calculated, %: C 68.00; H 6.93; N 5.66.

2-[(1-Phenylcyclopentyl)methylamino]ethanol hydrochloride (IV). A solution of 2.75 g (10 mmol) of amido ester **II** in 50 ml of benzene was added to a mixture of 1.5 g (40 mmol) of $LiAlH_4$ and 50 ml of anhydrous diethyl ether, and the mixture was heated for 12 h under reflux. When the reaction was complete, the mixture was treated with water and filtered, and the filtrate was evaporated. The residue was dissolved in anhydrous diethyl ether, a solution of HCl in diethyl ether was added, and the precipitate was filtered off and dried. Yield 1.5 g (65%), mp 148–150°C (from acetone), R_f 0.46 (benzene–acetone, 2:1, ammonia vapor). ^{1}H NMR spectrum, δ, ppm: 1.62–1.87 m and 1.98–2.19 m [4H each, $(CH_2)_4$], 2.79 m (2H, NC**H**$_2$CH$_2$), 3.15 s (2H, NC**H**$_2$), 3.63 m (2H, OCH_2), 5.07 t (1H, OH, J = 5.9 Hz), 7.15–7.30 m (5H, H_{arom}), 8.52 br.s (2H, NH, HCl). Found, %: C 65.62; H 8.80; Cl 13.95; N 5.39. $C_{14}H_{21}NO\cdot HCl$. Calculated, %: C 65.74; H 8.67; Cl 13.86; N 5.48.

Diamides Va–Vc (*general procedure*). A mixture of 10 mmol of amido ester **II** and 10 mmol of the corresponding amine was heated for 5 h at 35–40°C. The resulting solid material was treated with hexane, and the precipitate was filtered off, washed with water, 10% aqueous HCl, and water again, dried in air, and recrystallized from appropriated solvent.

***N*-Butyl-*N′*-(1-phenylcyclopentylmethyl)ethanediamide (Va).** Yield 70%, mp 108–110°C (from toluene), R_f 0.58 (benzene–acetone, 8:1). ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, CH_3, J = 7.2 Hz), 1.32 m (2H, C**H**$_2$CH$_3$), 1.48 m (C**H**$_2$CH$_2$CH$_3$), 1.66–2.02 m (8H, CH_2), 3.13 t.d (2H, NHC**H**$_2$CH$_2$, J = 6.8, 5.9 Hz), 3.35 d (2H, C**H**$_2$NH, J = 6.5 Hz), 7.18 m (1H) and 7.25–7.33 m (4H) (H_{arom}), 7.45 br.t (1H, CH$_2$N**H**, J = 6.5 Hz), 8.36 br.t (1H, BuN**H**, J = 6.5 Hz). Found, %: C 71.67; H 8.56; N 9.15. $C_{18}H_{26}N_2O_2$. Calculated, %: C 71.49; H 8.67; N 9.26.

2-Oxo-2-(pyrrolidin-1-yl)-*N*-(1-phenylcyclopentylmethyl)acetamide (Vb). Yield 60%, mp 106–108°C (from hexane), R_f 0.61 (benzene–acetone, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.63–2.01 m (12H, CH_2), 3.33 d (2H, NHC**H**$_2$, J = 6.4 Hz), 3.38 t and 3.69 t (2H each, NCH_2, J = 6.7 Hz), 7.17 m (1H) and 7.24–7.32 m (4H) (H_{arom}), 7.53 br.t (1H, NH, J = 6.4 Hz). Found, %: C 71.69; H 8.17; N 9.45. $C_{18}H_{24}N_2O_2$. Calculated, %: C 71.97; H 8.05; N 9.33.

2-(Morpholin-4-yl)-2-oxo-*N*-(1-phenylcyclopentylmethyl)acetamide (Vc). Yield 62%, mp 101–102°C (from heptane), R_f 0.53 (benzene–acetone, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.62–2.02 m (8H, CH_2); 3.22 m (2H), 3.45 m (4H), and 3.57 m (2H) (NCH_2CH_2O), 3.38 d (2H, NHC**H**$_2$, J = 6.3 Hz), 7.13 m (1H) and 7.21–7.31 m (4H, H_{arom}), 7.91 t (1H, NH, J = 6.3 Hz). Found, %: C 68.55; H 7.48; N 8.73. $C_{18}H_{24}N_2O_3$. Calculated, %: C 68.33; H 7.65; N 8.85.

Diamides **Vd** and **Ve** were synthesized in a similar way from 10 mmol of **II** and 10 mmol of 1,3,4-thiadi-

azol-2-amine or pyridin-4-amine by heating the reactant mixture for 10 h at 65–70°C.

***N*-(1-Phenylcyclopentylmethyl)-*N*′-(1,3,4-thiadiazol-2-yl)ethanediamide (Vd).** Yield 67%, white crystals, mp 190–191°C (from toluene), R_f 0.45 (benzene–acetone, 4:1). ^{1}H NMR spectrum, δ, ppm: 1.63–2.07 m (8H, CH_2), 3.44 d (2H, NCH_2, J = 6.5 Hz), 7.14–7.32 m (5H, H_{arom}), 7.97 t (1H, N**H**CH_2, J = 6.5 Hz), 9.05 s (1H, 5′-H), 12.72 br.s (1H, NH). Found, %: C 58.40; H 5.38; N 16.85; S 9.58. $C_{16}H_{18}N_4O_2S$. Calculated, %: C 58.16; H 5.49; N 16.96; S 9.70.

***N*-(1-Phenylcyclopentylmethyl)-*N*′-(pyridin-4-yl)ethanediamide (Ve).** Yield 61%, mp 163–165°C (from ethanol), R_f 0.41 (benzene–acetone, 2:1). ^{1}H NMR spectrum, δ, ppm: 1.65–2.07 m (8H, CH_2), 3.42 d (2H, NCH_2, J = 6.5 Hz), 7.15–7.31 m (5H, H_{arom}), 7.79 m (2H) and 8.37 m (2H) (pyridine), 7.82 t (1H, N**H**CH_2, J = 6.5 Hz), 10.83 s (1H, NH). Found, %: C 70.71; H 6.40; N 12.74. $C_{19}H_{21}N_3O_2$. Calculated, %: C 70.57; H 6.55; N 12.99.

Diamides Vf–Vi (*general procedure*). A mixture of 10 mmol of amido ester **II** and 10 mmol of 2-aminoethanol, 2-(morpholin-4-yl)ethanamine, (2-furyl)methanamine, or (1-phenylcyclopentyl)methanamine in 30 ml of ethanol was heated for 8 h under reflux. After cooling, the precipitate was filtered off.

***N*-(2-Hydroxyethyl)-*N*′-(1-phenylcyclopentylmethyl)ethanediamide (Vf).** Yield 62%, mp 132–133°C (from ethanol), R_f 0.58 (benzene–acetone, 1:1). ^{1}H NMR spectrum, δ, ppm: 1.63–2.02 m (8H, CH_2), 3.23 q (2H, NHC**H**$_2$$CH_2$, J = 5.7 Hz), 3.36 d (2H, NHC**H**$_2$, J = 6.5 Hz), 3.48 q (2H, OCH_2, J = 5.7 Hz), 4.43 t (1H, OH, J = 5.7 Hz), 7.18 m (1H) and 7.25–7.33 m (4H) (H_{arom}), 7.49 t (1H, N**H**CH_2, J = 6.5 Hz), 8.30 t (1H, N**H**CH_2CH_2, J = 5.7 Hz). Found, %: C 66.35; H 7.51; N 9.72. $C_{16}H_{22}N_2O_3$. Calculated, %: C 66.18; H 7.64; N 9.65.

***N*-[2-(Morpholin-4-yl)ethyl]-*N*′-(1-phenylcyclopentylmethyl)ethanediamide (Vg).** Yield 60%, mp 121–122°C (from ethanol), R_f 0.58 (benzene–acetone, 3:1). ^{1}H NMR spectrum, δ, ppm: 1.63–2.05 m (8H, CH_2), 2.38–2.47 m (6H, NC**H**$_2$$CH_2$), 3.26 q (2H, NHC**H**$_2$$CH_2$, J = 6.3 Hz), 3.31 d (2H, NHC**H**$_2$, J = 6.5 Hz), 3.58 m (4H, OCH_2), 7.15 m (1H) and 7.23–7.31 m (4H) (H_{arom}), 7.48 t (1H, N**H**CH_2, J = 6.5 Hz), 8.33 t (1H, N**H**CH_2CH_2, J = 6.3 Hz). Found, %: C 66.55; H 8.26; N 11.81. $C_{20}H_{29}N_3O_3$. Calculated, %: C 66.83; H 8.13; N 11.69.

***N*-(Furan-2-ylmethyl)-*N*′-(1-phenylcyclopentylmethyl)ethanediamide (Vh).** Yield 71%, mp 118–119°C (from toluene), R_f 0.58 (benzene–acetone, 4:1). ^{1}H NMR spectrum, δ, ppm: 1.63–1.98 m (8H, CH_2), 3.31 d (2H, NHC**H**$_2$, J = 6.5 Hz), 4.31 d (2H, NHC**H**$_2$Fu, J = 6.2 Hz), 6.17 d (1H, 3′-H, J = 3.2 Hz), 6.28 d.d (1H, 4′-H, J = 3.2, 2.8 Hz), 7.14 m (1H) and 7.21–7.31 m (4H) (H_{arom}), 7.36 d (1H, 5′-H, J = 1.8 Hz), 7.51 d (1H, N**H**CH_2, J = 6.5 Hz), 8.34 t (1H, N**H**CH_2Fu, J = 6.2 Hz). Found, %: C 69.70; H 6.90; N 8.70. $C_{19}H_{22}N_2O_3$. Calculated, %: C 69.92; H 6.79; N 8.58.

***N*,*N*′-Bis(1-phenylcyclopentylmethyl)ethanediamide (Vi).** Yield 71%, mp 160–161°C (from ethanol), R_f 0.66 (benzene–diethyl ether, 4:1). ^{1}H NMR spectrum, δ, ppm: 1.62–2.00 m (16H, CH_2), 3.31 d (4H, NHC**H**$_2$, J = 6.6 Hz), 7.14–7.31 m (10H, H_{arom}), 7.44 t (2H, NH, J = 6.6 Hz). Found, %: C 77.35; H 7.84; N 6.81. $C_{26}H_{32}N_2O_2$. Calculated, %: C 77.19; H 7.97; N 6.92.

Substituted anilides **VIIa**–**VIId** were synthesized as described above for amido ester **II**.

Ethyl 2-(3-bromophenylamino)-2-oxoacetate (VIIa). Yield 70%, mp 117–119°C (from ethanol), R_f 0.52 (benzene–diethyl ether, 3:1). IR spectrum, ν, cm^{-1}: 3328 (NH), 1725 (C=O, ester), 1708 (C=O, amide). Found, %: C 44.28; H 3.55; Br 29.20; N 5.29. $C_{10}H_{10}BrNO_3$. Calculated, %: C 44.14; H 3.70; Br 29.37; N 5.15.

Ethyl 2-(4-bromophenylamino)-2-oxoacetate (VIIb). Yield 74%, mp 155–156°C (from ethanol), R_f 0.50 (benzene–diethyl ether, 3:1). IR spectrum, ν, cm^{-1}: 3333 (NH), 1731 (C=O, ester), 1707 (C=O, amide). Found, %: C 44.28; H 3.55; Br 29.20; N 5.29. $C_{10}H_{10}BrNO_3$. Calculated, %: C 44.14; H 3.70; Br 29.37; N 5.15.

Ethyl 2-(4-fluorophenylamino)-2-oxoacetate (VIIc). Yield 71%, mp 110–112°C (from ethanol), R_f 0.51 (benzene–diethyl ether, 3:1). IR spectrum, ν, cm^{-1}: 3319 (NH), 1734 (C=O, ester), 1688 (C=O, amide). Found, %: C 56.75; H 4.89; F 8.91; N 6.75. $C_{10}H_{10}FNO_3$. Calculated, %: C 56.87; H 4.77; F 9.00; N 6.63.

Ethyl 2-oxo-2-(3-trifluoromethylphenylamino)-acetate (VIId). Yield 69%, mp 118–120°C (from ethanol), R_f 0.49 (benzene–diethyl ether, 3:1). IR spectrum, ν, cm^{-1}: 3337 (NH), 1710 (C=O, ester), 1699 (C=O, amide). Found, %: C 50.39; H 3.71; F 21.63; N 5.58. $C_{11}H_{10}F_3NO_3$. Calculated, %: C 50.58; H 3.86; F 21.82; N 5.36.

Ethyl 2-(2-methoxyphenylamino)-2-oxoacetate (VIIe) was synthesized according to the procedure described in [4].

Diamides **VIIIa**–**VIIIe** were synthesized as described above for amides **V** by heating a mixture of 10 mmol of amine **I** and amido ester **VIIa**–**VIIe** at 65–70°C; the products were recrystallized from ethanol.

***N*-(3-Bromophenyl)-*N′*-(1-phenylcyclopentylmethyl)ethanediamide (VIIIa).** Yield 60%, mp 146–148°C, R_f 0.70 (benzene–acetone, 8:1). ^{1}H NMR spectrum, δ, ppm: 1.65–2.07 m (8H, CH_2), 3.43 d (NHC**H**$_2$, J = 6.5 Hz), 7.19 m (1H) and 7.27–7.31 m (4H) (H_{arom}); 7.33 m (1H), 7.44 t (1H, J = 8.0 Hz), 8.04 m (1H), and 8.28 t (1H, J = 2.0 Hz) (C_6H_4); 7.74 t (1H, N**H**CH_2, J = 6.5 Hz), 10.81 s (1H, N**H**Ar). Found, %: C 59.69; H 5.42; Br 19.79; N 7.12. $C_{20}H_{21}BrN_2O_2$. Calculated, %: C 59.86; H 5.27; Br 19.91; N 6.98.

***N*-(4-Bromophenyl)-*N′*-(1-phenylcyclopentylmethyl)ethanediamide (VIIIb).** Yield 59%, mp 159–160°C, R_f 0.70 (benzene–acetone, 8:1). ^{1}H NMR spectrum, δ, ppm: 1.65–2.06 m (8H, CH_2), 3.42 d (2H, NHC**H**$_2$, J = 6.5 Hz), 7.18 m (1H) and 7.26–7.33 m (4H) (H_{arom}), 7.37 m and 7.78 m (2H each, C_6H_4), 7.71 t (1H, N**H**CH_2, J = 6.5 Hz), 10.55 s (1H, N**H**Ar). Found, %: C 59.71; H 5.40; Br 19.75; N 7.10. $C_{20}H_{21}BrN_2O_2$. Calculated, %: C 59.86; H 5.27; Br 19.91; N 6.98.

***N*-(4-Fluorophenyl)-*N′*-(1-phenylcyclopentylmethyl)ethanediamide (VIIIc).** Yield 57%, mp 140–142°C, R_f 0.70 (benzene–acetone, 8:1). ^{1}H NMR spectrum, δ, ppm: 1.65–2.02 m (8H, CH_2), 3.40 d (2H, NHC**H**$_2$, J = 6.5 Hz), 7.18 m (1H) and 7.27–7.32 m (4H) (H_{arom}), 7.37 m and 7.77 m (2H each, C_6H_4), 7.70 t (1H, N**H**CH_2, J = 6.5 Hz), 10.54 s (1H, N**H**Ar). Found, %: C 70.45; H 6.14; F 5.69; N 8.14. $C_{20}H_{21}FN_2O_2$. Calculated, %: C 70.57; H 6.22; F 5.58; N 8.23.

***N*-(1-Phenylcyclopentylmethyl)-*N′*-(3-trifluoromethylphenyl)ethanediamide (VIIId).** Yield 61%, mp 134–136°C, R_f 0.67 (benzene–acetone, 8:1). ^{1}H NMR spectrum, δ, ppm: 1.65–2.07 m (8H, CH_2), 3.43 d (2H, NHC**H**$_2$, J = 6.5 Hz), 7.19 m (1H) and 7.28–7.32 m (4H) (H_{arom}); 7.33 m (1H), 7.44 t (1H, J = 8.0 Hz), 8.04 m (1H), and 8.28 t (1H, J = 2.0 Hz) (C_6H_4); 7.74 t (1H, N**H**CH_2, J = 6.5 Hz), 10.81 s (1H, N**H**Ar). Found, %: C 64.75; H 5.36; F 14.78; N 7.05. $C_{21}H_{21}F_3N_2O_2$. Calculated, %: C 64.61; H 5.42; F 14.60; N 7.18.

***N*-(2-Methoxyphenyl)-*N′*-(1-phenylcyclopentylmethyl)ethanediamide (VIIIe).** Yield 65%, mp 116–118°C, R_f 0.64 (benzene–acetone, 8:1). ^{1}H NMR spectrum, δ, ppm: 1.64–2.06 m (8H, CH_2), 3.42 d (2H, NHC**H**$_2$, J = 6.5 Hz), 3.95 s (3H, OCH_3); 6.90 m (1H), 6.96 d.d (1H, J = 8.3, 1.6 Hz), 7.06 m (1H), and 8.24 d.d (1H, J = 8.0, 1.8 Hz) (C_6H_4); 7.19 m (1H) and 7.27–7.33 m (4H) (H_{arom}), 7.76 t (1H, N**H**CH_2, J = 6.5 Hz), 9.66 s (1H, N**H**Ar). Found, %: C 71.79; H 6.75; N 7.87. $C_{21}H_{24}N_2O_3$. Calculated, %: C 71.57; H 6.86; N 7.95.

The IR spectra were recorded on a Nicolet Avatar 330 FT-IR spectrometer from samples dispersed in mineral oil. The ^{1}H NMR spectra were measured on a Varian Mercury-300 spectrometer from solutions in DMSO-d_6 using tetramethylsilane as internal reference. The melting points were determined using a Boetius micro-hot stage. TLC analyses were carried out on Silufol UV-254 plates; spots were visualized by treatment with iodine vapor.

REFERENCES

1. Agekyan, A.A., Solomina, L.P, Pirdzhanov, L.Sh., and Markaryan, E.A., *Arm. Khim. Zh*., 1995, vol. 48, nos. 1–3, p. 88; Agekyan, A.A., Mkryan, G.G., Gukasyan, T.G., Tsatinyan, A.S., Shirinyan, E.A., Asatryan, T.O., Markaryan, K.Zh., Grigoryan, A.V., and Markaryan, E.A., *Khim. Zh. Arm*., 2011, vol. 63, p. 398; Agekyan, A.A., Mkryan, G.G., Tsatinyan, A.S., Noravyan, O.S., Gukasyan, T.G., Shirinyan, E.A., and Markaryan, E.A., *Khim. Zh. Arm*., 2011, vol. 64, p. 531.
2. Mndzhoyan, A.L. and Tatevosyan, G.T., *Izv. Akad. Nauk Arm. SSR, Ser. Khim. Nauk*, 1958, vol. 17, no. 2, p. 93.
3. Lambert, J.B., Huseland, D.E., and Gen-Tai Wang, *Synthesis*, 1986, p. 657.
4. Vartanyan, S.O., Avakyan, A.S., Sarkisyan, A.B., Markaryan, E.A., Arutyunyan, S.A, Shirinyan, E.A., and Khachatryan, A.G., *Vestn. MANEB*, 2005, vol. 10, no. 6, p. 198.