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# Synthesis of some Adamantane Fragment Containing New Dipeptides Via Ugi Reaction on the Basis of Isocyanide

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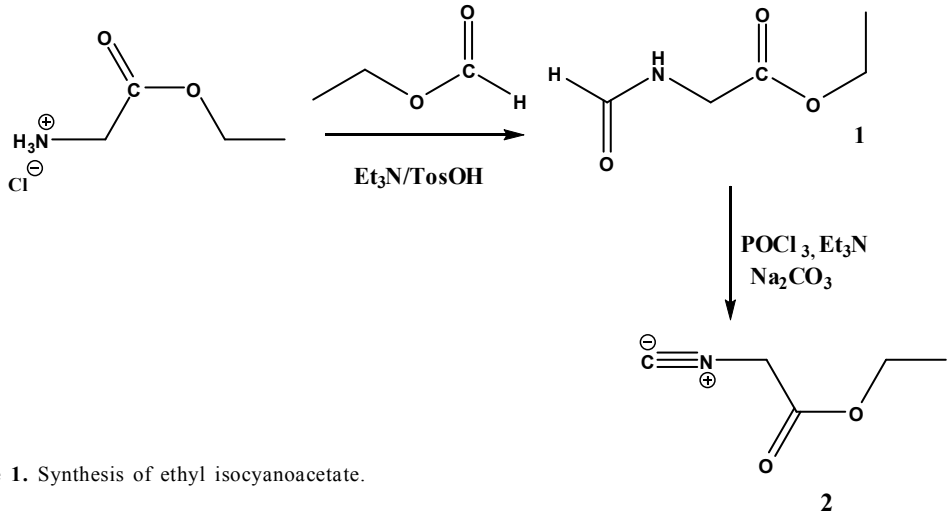
**ABSTRACT. Some adamantane fragment containing dipeptides were synthesized on the basis of isocyanides via Ugi reaction. Adamantane-1-carboxylic acid, different aryl- and alkylamines, aldehydes and adamantane-2-on, ethyl isocyanoacetate and benzene isocyanide are used as reacting components. Structures of the synthesized compounds are determined by the NMR and mass-spectrometry data.**


***Key words:*** *multicomponent reaction, Ugi reaction, peptides, adamantane-1-carboxylic acid, adamantanone, amines, aldehydes, isocyanides.*

As is known, peptides are biologically active substances. They are presented in all the living cells of the organisms. They participate and control many biochemical and physiological processes. Over the last few years peptides, as therapeutical means, were broadly produced. The use of peptides in medicine is of wide interest. Preparations synthesized on the basis of peptides are used in neurology, endocrynology and hematology [1].

Many methods for synthesis of peptides are known but multicomponent reaction (MCR) on the basis of isocyanides named as the Ugi reaction is the most interesting [2-8].

It should be noted that adamantane fragment containing organic compounds are widely used in the medicine due to their unique pharmacological properties. Preparations of the adamantane series (amantadine, amantol, simmetrel, mantadix, rimantadine, paramantine, protexin, viregite, betsovet, neoride, bromantane, kemantane, etc.) are characterized with antiviral, antibacterial, anticytotoxic, psycho neuro immuno regulatory and other effects. The presence of adamantane radicals in molecules of medicinal preparations enhances their activity and depresses the toxicity [9]. They restore functional activities of nervous, hormonal and immune systems and also




**Scheme 1.** Synthesis of ethyl isocyanoacetate.

increase mental and physical capacities and resistance of organisms to viral and bacterial infections [9-15]. Because of wide spectrum activity of adamantane fragment containing compounds the study of synthesis and investigation of biological activity of adamantane fragment containing peptides obtained via Ugi reaction on the basis of isocyanide is the most interesting [16-21].

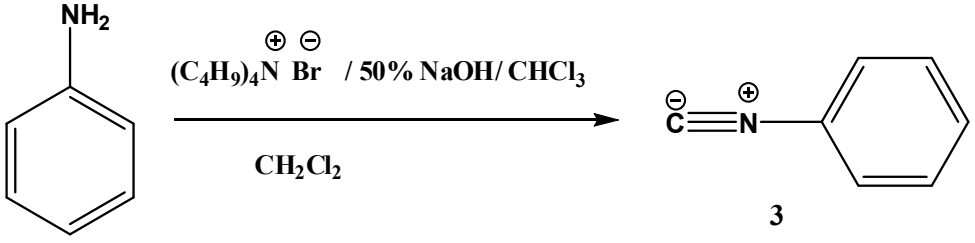
The object of our study was the synthesis of adamantane fragment containing dipeptides using adamantane-1-carboxylic acid, 1-aminoadamantane and adamantane-2-on.

The formation of ethyl isocyanoacetate is known to be a two-step process. The first step in the reaction is preparation of N-formylglycine ethyl ester. Treatment of ethyl formate with glycine ethyl ester hydrochloride at the presence of triethylamine and *p*-toluene sulfonic acid monohydrate at high temperature leads to formation of N-formylglycine ethyl ester (1) colorless oil with 92 % yield.

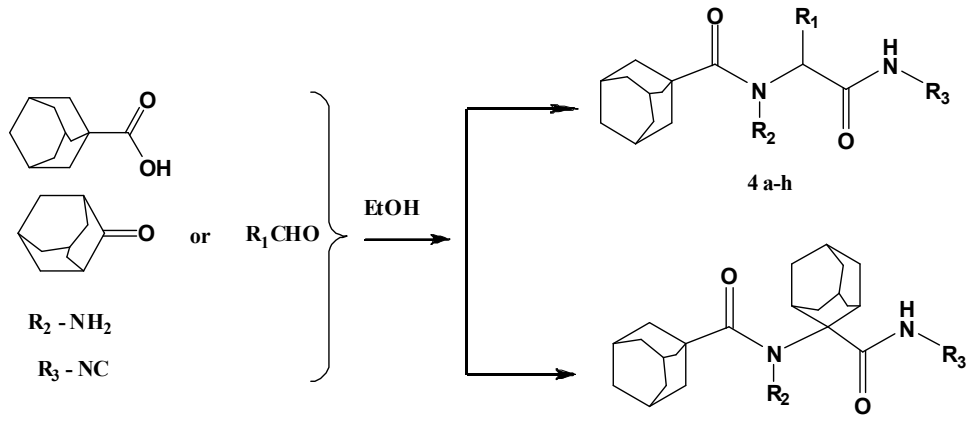
The second stage is formation of ethyl isocyanoacetate. By interaction of phosphorus (V) oxychloride ($POCl_3$) with the N-formyl glycine ethyl ester (1) in the area of dichloromethane at the presence of triethylamine at low temperature and further treating it with $Na_2CO_3$ the colorless oil dilution of ethyl isocyanoacetate (2) was obtained with 51 % yield [22] (Scheme 1).

Benzene isocyanide was obtained with 44 % yield by interaction of aniline with 50% sodium alkali and chloroform in the area of dichloromethane at the presence of tetrabutylammonium bromide at low temperature (Scheme 2).

The Ugi four-component reaction (Ugi 4CR) was conducted by condensation of aldehyde or adamantane-2-on with amine, adamantane-1-carboxylic acid and isocyanide at 0-60 $^0$C temperature in the area of ethanol. The reaction mixture was stirred for 20 h and then dichloromethane was added, quaked with saturated $NaHCO_3$ and washed with 1M $KHSO_4$ solution. The organic phase was concentrated and chromatically purified on the column by standard method ($SiO_2$, petroleum/ethylacetate), dipeptides 4a-h and 5a, b (Scheme 3) was obtained with 42-64 % yeild [24] (Table 1).




**Scheme 2.** Synthesis of benzene isocyanide.




**Scheme 3.** Synthesis of dipeptides Ugi 4CR.

Structures of the obtained compounds were determined by the $^{1}H$ and $^{13}C$ NMR and mass-spectroscopy.

## Experimental part

The progress of reaction and purity of synthesized compounds were checked on the „Silica gel TLC PET-foils". $^{1}H$ and $^{13}C$ nuclear magnetic resonance spectra were recorded by the spectrometer Bruker at 400 and 100 Hz, respectively. Mass-spectrum analysis was fulfilled with the device MAT 95 v.Finnigan (USA). Silicon dioxide (nanopowder, particle sizes 10-20 nm) was used as stationary phase for column chromatography. Petroleum/ethylacetate mixture of different ratio was used as the eluant.

**N-formylglycine ethyl ester (1).** 14 g ( 0.1 mol) of glycine ethyl ester hydrochloride and 0.01 g (0.00006 mol) *p*-toluene sulphonic acid monohydrate were dissolved in 50 ml ethyl formate and then 11.1 g (0.11 mol) triethylamine was added by drop wise. Reaction mixture was stirred at high temperature for 20 h and monitored by TLC (hexane/ethylacetate 4/1). Reaction mixture was cooled from 20 °C to 0, -5 $^{0}$C. The filtrate was concentrated and distilled under the reduced pressure. 8.7 g (92 %) of colorless oil of N- formylglycinethyl ester (1) was obtained [22].

**Ethylisocyanoacetate (2).** 7.1 g (54.16 mmol) of N-formyl glycinethylester was dissolved at cooling in 150 ml of dichloromethane; afterwards 13.6 g (134.3 mmol) of triethylamine was added by drop wise under stirring for 1 hrs. Then 10.83 g of $Na_2CO_3$ in 51 ml of water was added at the room temperature under stirring for 30 min. The reaction mixture was diluted with 300 ml of water and was extracted $CH_2Cl_2$ (2 x 75 ml). The organic phase was washed with the saturated NaCl-solution, was dried over anhydrous $K_2CO_3$. After filtration the organic layer was concentrated in vacuum and distilled. 3.11g (51 %) of

**Table 1. Peptides obtained by Ugi reaction with isocyanides**

| | $R_1$ | $R_2$ | $R_3$ | T, °C | Y, % |
|---|---|---|---|---|---|
| 4a | - i-$C_3H_7$ | $C_6H_5CH_2$- | -$CH_2COOC_2H_5$ | 50 | 54 |
| 4b | - i-$C_3H_7$ | -$C_6H_5$ | -$CH_2COOC_2H_5$ | room t. | 46.3 |
| 4c | - i-$C_3H_7$ | $C_6H_5CH_2CH_2$ - | -$CH_2COOC_2H_5$ | 50 | 43 |
| 4d | -$C_4H_9$ | - i-$C_3H_7$ | -$CH_2COOC_2H_5$ | room t. | 55 |
| 4e | -$C_4H_9$ | -$C_6H_5$ | -$CH_2COOC_2H_5$ | room t. | 60 |
| 4f | -$C_4H_9$ | $C_6H_5CH_2CH_2$ - | - $CH_2COOC_2H_5$ | 35 | 57 |
| 4g | -$C_4H_9$ | - $C_4H_9$ | -$CH_2COOC_2H_5$ | 50 | 43 |
| 4h | - i-$C_3H_7$ | -$C_{10}H_{15}$ | -$C_6H_5$ | 60 | 64 |
| 5a | - | $C_6H_5CH_2$- | -$CH_2COOC_2H_5$ | 50 | 43 |
| 5b | - | -$C_6H_5$ | -$CH_2COOC_2H_5$ | room t. | 42 |

colorless oil was obtained.

**Benzene isocyanide (3).** 2 ml (22 mmol) of aniline was diluted in 100 ml of dichloromethane, then 50 ml of 50 % NaOH dilution in water was added. 0.07 g (0.22 mmol) of tetrabutyl ammonium bromide and 2.6 ml (33 mmol) chloroform were added. The mixture was stirred for 6 h at room temperature and afterwards 200 ml of water was added. Organic phase was separated through the separation funnel, washed twice with 100 ml of water and 100 ml of the saturated brine, was dried over $MgSO_4$ and filtered and concentrated in vacuum. The obtained product was purified on the chromatography column by a standard method (combination of dichloromethane/hexane 4/1 and $SiO_2$). Yellow viscous oil mass with the yield 0.97 g (41 %) was obtained [23].

**Preparation of 4a.** 0.214 g (2 mmol) of benzylamine and 0.18 ml (2 mmol) of isobutylaldehyde were dissolved in 4 ml ethanol at room temperature and the mixture was stirred for 15 min. First, 0.36 g (2 mmol) of Ad COOH was added and heated up to 45 - 50 °C and afterwards, 0.23 ml (2 mmol) of ethyl isocyano acetate was added and reaction mixture stirred overnight at the 50 °C for 15 h. The reaction mixture was diluted with dichloromethane and quaked with saturated $NaHCO_3$ solution. Afterwards the removing solvent was washed with 1 mol $KHSO_4$-solution and was dried over $Na_2SO_4$. Then organic layer was filtered and concentrated in vacuum affording a product as a yellowish oil. The obtained product was purified on the chromatography column by the standard method ($SiO_2$, petroleum/ethylacetate, 4/1). 0.49 g (54 %) of yellowish oil was obtained. $R_f$ = 0.24 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.87 (3H, d, *J* = 6.4, $\underline{CH_3}CHCH_3$), 0.88 (3H, d, *J* = 6.4, $CH_3CH\underline{CH_3}$),1.28(3H, t, *J*=7.2, -$OCH_2\underline{CH_3}$), 1.71 (6H, m, H Ad), 2.04 - 2.14 (9H, m, H Ad),2.73 (1H, m, $\underline{CH}(CH_3)_2CH$-),4.19 (2H, q, *J*=7.2, -$O\underline{CH_2}CH_3$), 4.89 (1H, d, *J* = 16.4, -N(CO)$\underline{CH}$-$CH(CH_3)_2$), 7.27- 7.32 (3H, m, H Ar), 7.21 - 7.23 (2H, m, H Ar),7.96 (1H, s, NH).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm:14.16 (1C, -$OCH_2\underline{CH_3}$), 19.49 (1C, $CH_3CH\underline{CH_3}$), 20.12 (1C, $\underline{CH_3}CHCH_3$), 26.67 (1C, $CH_3\underline{CH}CH_3$), 28.43 (3C Ad), 36.42 (3C Ad), 39.66 (3C Ad), 40.92 (1C Ad), 43.31 (1C, -NH$\underline{CH_2}$C=O), 52.76 (1C, -N$\underline{CH_2}C_6H_5$), 61.06 (1C, -N$\underline{CH}$C=O), 71.42 (1C, -$O\underline{CH_2}CH_3$), 127.47 (2C Ar), 127.62 (1C Ar), 128.37 (2C Ar), 136.49 (1C Ar), 169.74 (C=O), 171.25 (C=O), 180.25 (C=O).

Mass-spectrum 4a: found: *m*/*z* 454.2695[M]$^+$. $C_{28}H_{36}N_2O_2$. Calculated *m*/*z*: 454.2777.

**Preparation of 4b.** 0.19 ml (2 mmol) of aniline, 0.18 ml (2 mmol) of isobutyl aldehyde, 0.36 g (2 mmol) of AdCOOH and 0.23 ml (2 mmol) of ethylisocyanide were dissolved in 2 ml ethanol and reaction was carried out by the above-mentioned method at the room temperature and the obtained product was purified on the chromatography column ($SiO_2$, petroleum/ethylacetate, 5/1) 0.42 g (46.3 %) of yellowish oil was obtained. $R_f$ = 0.24 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.94 (3H, d, *J* = 6.4, $\underline{CH_3}CHCH_3$), 1.10 (3H, d, *J* = 6.4, $CH_3CH\underline{CH_3}$), 1.29 (3H, t, *J* = 7.2, -$OCH_2\underline{CH_3}$), 1.46 - 1.57 (6H, m, H Ad), 1.65 - 1.76 (6H, m, H Ad), 1.79 - 1.85 (3H, m, H Ad), 2.60 (1H, m, $(CH_3)_2\underline{CH}CH$(CO) N-), 4.22 (2H, q, *J*= 7.2, -$O\underline{CH_2}CH_3$), 7.18 - 7.26 (2H, m, H Ar), 7.31 - 7.37 (3H, m, H Ar), 8.19 (1H, s, NH).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm:14.19 (1C, -$OCH_2\underline{CH_3}$), 19.82 (1C, $\underline{CH_3}CHCH_3$), 20.36 (1C, $CH_3CH\underline{CH_3}$), 26.65 (1C, $CH_3\underline{CH}CH_3$), 28.31 (3C Ad), 36.26 (1C Ad), 40.25 (3C Ad), 40.86(3C Ad), 44.76 (1C, -NH$\underline{CH_2}$C=O), 61.14 (2C, -$O\underline{CH_2}CH_3$ and -N$\underline{CH}$C=O), 128.41 (2C Ar), 128.85(1C Ar), 129.30 (1C Ar), 129.59 (2C Ar), 169.95 (C=O), 171.27 (C=O), 180.69 (C=O).

Mass-spectrum 4b: found: *m*/*z* 440.267[M]$^+$. $C_{28}H_{36}N_2O_2$. Calculated *m*/*z*: 440.2675.

**Preparation of 4c.** The synthesis was fulfilled by analogy of 4 a-synthesis. The mixture of 0.25 ml (2 mmol) of phenethylamine, 0.18 ml (2 mmol) of isobutyl aldehyde, 0.36 g (2 mmol) of AdCOOH

and 0.23 ml (2 mmol) of ethylisocyanide by heating in 7 ml of ethanol up to 50 °C by the above-described method and by purification on the chromatography column ($SiO_2$, petroleum/ethylacetate, 5/1) 0.4 g (43 %) of yellow oil was obtained. $R_f$ = 0.31 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz) : 0.84 (3H, d, *J* = 6.8,$CH_3CH\underline{CH_3}$), 1.03 (3H, d, *J* = 6.8, $\underline{CH_3}CHCH_3$), 1.26 (3H, t,*J* = 7.2, -$OCH_2\underline{CH_3}$), 1.69 - 1.78 (6H, m, HAd), 2.19 - 1.97 (9H, m, H Ad), 2.74 (1H, m, $(CH_3)_2\underline{CH}$CH-), 2.93 (2H, m, $C_6H_5\underline{CH_2}CH_2$N-), 3.71 (2H, m,$C_6H_5CH_2\underline{CH_2}$N-),3.78 (1H, d, *J* = 10.8, -N$\underline{CH}$(CO)$CH(CH_3)_2$), 4.17 (2H, q, *J* = 7.2, -$O\underline{CH_2}CH_3$), 7.18 - 7.24 (3H, m, H Ar), 7.28 - 7.32 (2H, m, H Ar), 8.15 (1H, s, NH).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm:14.15 (1C, -$OCH_2\underline{CH_3}$), 19.26 (1C, $CH_3CH\underline{CH_3}$), 20.27 (1C, $\underline{CH_3}CHCH_3$), 26.37(1C, $CH_3\underline{CH}CH_3$), 28.47 (3C Ad), 35.58 (1C, $C_6H_5\underline{CH_2}CH_2$N-), 36.52 (4C Ad), 39.34 (3C Ad), 41.09 (1C, -NH$\underline{CH_2}$C=O), 43.09 (1C, $C_6H_5CH_2\underline{CH_2}$N-), 61.08 (2C, -$O\underline{CH_2}CH_3$ and -N$\underline{CH}$C=O), 126.57 (1C Ar), 128.57(2C Ar), 128.70 (2C Ar), 138.32 (1C Ar), 169.58 (C=O),172.70 (C=O), 179.57 (C=O).

Mass-spectrum 4c: found: *m*/*z* 468.2912 $[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m*/*z*: 468.2988

**Preparation of 4d.** The synthesis was fulfilled by analogy of 4a-synthesis. Reacting between 0.20 ml (2 mmol) of butylamine, 0.18 ml (2 mmol) of isobutyl aldehyde, 0.36 g (2 mmol) of AdCOOH and 0.23 ml (2 mmol) of ethylisocyanide in 4 ml of ethanol at the room temperature by the above-described method and purifying on the chromatography column ($SiO_2$, petroleum/ethylacetate, 9/1) 0.63 g (55 %) of yellowish oil was obtained. $R_f$ = 0.32 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.82 (3H, d, *J* = 6.8, $\underline{CH_3}CHCH_3$), 0.93 (3H, t, *J* = 7.2, -$N(CH_2)_3\underline{CH_3}$), 0.98 (3H, d, *J* = 6.8, $CH_3CH\underline{CH_3}$), 1.26 (3H, t, *J* = 7.2, -$OCH_2\underline{CH_3}$), 1.26 - 1.33 (2H, m, -$CH_2\underline{CH_2}CH_3$), 1.61 (2H, m, -$CH_2\underline{CH_2}CH_2$-), 1.72 (7H, m, H Ad), 2.01 - 2.06 (8H, m, H Ad), 2.73 (1H, m, $CH_3\underline{CH}CH_3$), 3.75 - 3.79 (5H,m), 4.17 (2H, q, *J* = 7.2, -$O\underline{CH_2}CH_3$), 8.30 (1H, s, NH).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm :13.69 (1C, -$N(CH_2)_3\underline{CH_3}$), 14.17 (1C, -$OCH_2\underline{CH_3}$), 19.47 (1C, $\underline{CH_3}CHCH_3$), 20.08 (1C, $CH_3CH\underline{CH_3}$), 20.23 (1C, -$N(CH_2)_2\underline{CH_2}CH_3$), 26.47 (1C, $(CH_3)_2\underline{CH}$CH-), 28.49 (3C Ad), 30.92 (1C, -$NCH_2\underline{CH_2}CH_2CH_3$), 31.08 (1C Ad), 36.56 (3C Ad), 39.19 (3C Ad), 41.08 (1C, -NH$\underline{CH_2}$C=O), 42.94 (1C, -N$\underline{CH_2}(CH_2)_2CH_3$), 54.35 (1C, $(CH_3)_2$CH-$\underline{CH}$=), 61.04 (1C, -$O\underline{CH_2}CH_3$), 169.65 (C=O), 172.91 (C=O), 173.56 (C=O).

Mass-spectrum 4d: found: *m*/*z* 420.2991$[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m*/*z*: 420.2988.

**Preparation of 4e.** The synthesis was fulfilled by analogy of 4a-synthesis. Reacting between 0.18 ml (2 mmol) of aniline, 0.21 ml (2 mmol) pentanal, 0.36 g (2 mmol) of AdCOOH and 0.23 ml (2 mmol) of ethyl isocyanoacetate in 2 ml of ethanol at the room temperature by the above-described method and chromatography on the $SiO_2$ column (petroleum/ethylacetate, 5/1) 0.56 g (60 %) of yellowish oil was obtained. $R_f$ = 0.37 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz):0.86 (3H, m, $\underline{CH_3}(CH_2)_3$-), 1.29 (3H, t,*J* = 7.2, -$OCH_2\underline{CH_3}$), 1.30 - 1.33 (4H, m),1.51 - 1.60 (8H, m, 6HAd and 2H, -$CH\underline{CH_2}CH_2CH_3$), 1.71 - 1.72 (6H, m, H Ad), 1.83 (3H, m, H Ad), 4.12 (2H, q, *J* = 7.2, -$O\underline{CH_2}CH_3$), 4.23 (2H, s, -NH$\underline{CH_2}$C=O), 4.99 (1H, t, *J* = 7.2,-N(CO)$\underline{CH}CH_2$-), 7.42 - 7.51 (3H, m, H Ar), 7.35 - 7.32 (2H, m, H Ar), 8.67 (1H, s, NH).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 13.95 (1C, -$CH(CH_2)_3\underline{CH_3}$), 14.18 (1C, -$OCH_2\underline{CH_3}$), 22.54 (1C, -$CH(CH_2)_2\underline{CH_2}CH_3$), 28.12 (1C, -$CHCH_2\underline{CH_2}CH_2CH_3$), 28.29 (3C Ad), 28.65 (1C, -$CH\underline{CH_2}(CH_2)_2CH_3$), 36.24 (3C Ad), 39.93 (1C Ad), 40.01 (3C Ad), 41.00 (1C, -NH$\underline{CH_2}$C=O), 61.22 (2C,-$O\underline{CH_2}CH_3$ and -N$\underline{CH}$(C=O)$CH_2$-), 128.67 (2C Ar), 130.80 (3C Ar), 139.31 (1C Ar), 169.93 (C=O), 171.60 (C=O), 179.85 (C=O).

Mass-spectrum **4e**: found: *m*/*z* 454.2867 $[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m*/*z*: 454.2832.

**Preparation of 4f.** 0.25 ml (2 mmol) of phenethyl

amine, 0.21 ml (2 mmol) of pentanal, 0.36 g (2 mmol) of AdCOOH and 0.23 ml (2 mmol) of ethyl isocyano acetate in the 7 ml of ethanol at 30-35°C by the above-described method and chromatography on the $SiO_2$ column (petroleum /ethyl acetate, 9/1) 0.55 g (57 %) of yellow oil was isolated. $R_f$=0.29 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz):0.90 (3H, t, *J*=7.2, -CH$(CH_2)_2CH_2\underline{CH_3}$), 1.19 - 1.26 (2H, m, -CHCH$_2\underline{CH_2}CH_2CH_3$), 1.25 (3H, t, *J*=7.2, -OCH$_2\underline{CH_3}$), 1.33 (2H, m, -CH$(CH_2)_2\underline{CH_2}CH_3$), 1.62 - 1.93(8H, m, H Ad and 2H, m, -CH$\underline{CH_2}(CH_2)_2CH_3$), 1.93 - 2.20 (7H, m, H Ad), 2.80 (2H, t, *J* = 6.8, $C_6H_5\underline{CH_2}CH_2$N-), 3.55 (2H, m, $C_6H_5CH_2\underline{CH_2}$N-), 4.17 (2H, q, *J*=7.2, -O$\underline{CH_2}CH_3$), 4.58 (1H, m, -N$\underline{CH}$(CO)$CH_2$-), 7.17 - 7.19 (2H, m, H Ar), 7.22 - 7.24 (1H, m, H Ar), 7.30 - 7.33 (2H, m, H Ar), 8.13(1H, s, $\underline{NH}$CO).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm : 13.97 (1C, -CH$(CH_2)_3\underline{CH_3}$), 14.16 (1C, -OCH$_2\underline{CH_3}$), 22.56 (1C, -CH$(CH_2)_2\underline{CH_2}CH_3$), 27.85 (1C, -CHCH$_2\underline{CH_2}CH_2CH_3$), 28.46 (3C Ad), 28.88 (1C, -CH$\underline{CH_2}(CH_2)_2CH_3$),30.93 (1C, Ar$\underline{CH_2}CH_2$N-), 36.52 (3C Ad), 39.21 (1C Ad), 39.33 (3C Ad), 41.26 (1C, -NH$\underline{CH_2}$C=O), 42.81 (1C, Ar$CH_2\underline{CH_2}$N-), 61.25(1C, -O$\underline{CH_2}CH_3$), 65.70 (1C, -N$\underline{CH}(CH_2)$C=O), 126.58 (1C Ar), 128.58 (1C Ar), 128.62 (1C Ar), 128.72 (2C Ar), 141.22 (1C Ar), 171.84 (C=O), 173.01 (C=O),176.38 (C=O).

Mass-spectrum 4f: found: *m*/*z* :483.2600 $[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m*/*z*: 483.3200.

**Preparation of 4g.** The synthesis was carried out by analogy of 4a-synthesis. Reacting between 20 ml (2 mmol) of *n*-butylamine, 0.18 ml (2 mmol) of pentanal, 0.36 g (2 mmol) of AdCOOH and 0.23 ml (2 mmol) of ethyl isocyanoacetate at 40-45 °C in the 7 ml of ethanol. 0.41 g (43 %) of yellow oil was isolated by the above-described method and chromatography on the $SiO_2$ column (petroleum/ ethylacetate, 4/1). $R_f$ = 0.29 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.89 (3H, m, $\underline{CH_3}(CH_2)_3$N-), 0.92 (3H, m, $\underline{CH_3}(CH_2)_3$CH-), 1.26 (2H, m, -CHCH$_2\underline{CH_2}CH_2CH_3$), 1.29 (2H, m, -OCH$_2\underline{CH_3}$), 1.30 - 1.34 (2H, m, -N$(CH_2)_2\underline{CH_2}CH_3$ and 2H, m, -CH$(CH_2)_2\underline{CH_2}CH_3$), 1.51 (2H, m, -NCH$_2\underline{CH_2}CH_2CH_3$ ),1.63 - 1.79 (5H, m, H Ad and 2H, m, -CH$\underline{CH_2}(CH_2)_2CH_3$), 1.84 (2H, m, H Ad), 1.92 (1H, m, H Ad), 1.99 - 2.09 (7H, m, H Ad), 3.24 (2H, t, *J* = 7.2, -N$\underline{CH_2}(CH_2)_2CH_3$), 4.18 (2H, q, *J* = 7.2, -O$\underline{CH_2}CH_3$), 4.40 (1H, m, -N(CO)$\underline{CH}CH_2$-), 5.55 (1H, s, NH).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 13.67 (1C, $\underline{CH_3}(CH_2)_3$N-), 13.97(1C, $\underline{CH_3}(CH_2)_3$CH-), 14.16 (1C, $\underline{CH_3}CH_2$O-), 20.26 (1C, $CH_3\underline{CH_2}(CH_2)_2$N-), 22.20 (1C, $CH_3\underline{CH_2}(CH_2)_2$CH-), 28.12 (1C, $CH_3CH_2\underline{CH_2}CH_2$CH-), 28.47 (3CAd), 28.63 (1C, $CH_3(CH_2)_2\underline{CH_2}$CH-), 31.10(1C, $CH_3CH_2\underline{CH_2}CH_2$ N-),36.54 (3CAd), 39.19 (3CAd), 39.29(1CAd), 41.22 (1C, -NH$\underline{CH_2}$C=O), 42.69(1C, $CH_3(CH_2)_2\underline{CH_2}$N-), 61.17(1C, -N$\underline{CH}$C=O), 61.21 (1C, -O$\underline{CH_2}CH_3$),169.67 (C=O), 176.06(C=O), 179.09(C=O).

Mass-spectrum 4g: found: *m*/*z* : 434.3119$[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m*/*z*: 434.3145.

**Preparation of 4h.** The synthesis was carried out at 45-60 °C. The reaction between 0.30 g (2 mmol) of 1-aminoadamantane, 0.18 ml (2 mmol) of isobutyl aldehyde, 0.36 g (2 mmol) of AdCOOH and 0.25 ml (2 mmol) of benzene isocyanide in 12 ml of alcohol was carried out by the above-described method and chromatography on the $SiO_2$ column (petroleum/ethylacetate, 9/1). 0.41 g (43 %) of yellow oil was obtained. $R_f$ = 0.29 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 0.90 (6H, d, *J* = 7.2, $\underline{CH_3}CHCH_3$ and $CH_3CH\underline{CH_3}$), 1.67-1.79 (10H, m, H Ad), 1.86-1.91 (9H, m, H Ad), 2.02 (8H, m, H Ad), 2.10 (3H, m, H Ad), 2.44 (1H, m, -CH$\underline{CH}(CH_3)_2$), 5.23 (1H, d, *J*=4, -N$\underline{CH}$CH$(CH_3)_2$), 7.05-7.21(1H, m, HAr),7.32-7.36 (2H, m, H Ar), 7.49-7.52 (1H, m, H Ar), 7.59-7.61 (1H, m, HAr), 7.67 (1H, s, SNH).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm : 18.90 (1C, $\underline{CH_3}CHCH_3$),19.60 (1C, $CH_3CH\underline{CH_3}$), 27.82 (3C Ad), 27.96 (3C Ad), 29.41 (1C, $CH_3\underline{CH}CH_3$), 36.34 (3C Ad), 36.42 (1C Ad), 36.52 (3C Ad), 38.81 (3C Ad), 38.98 (3C Ad), 59.98 (1C, -N$\underline{CH}$(C=O)CH$(CH_3)_2$), 60.16 (1C, Ad), 119.82 (1C Ar), 124.71(1C Ar), 128.95(1C Ar), 129.09

(2C Ar), 136.93(1C Ar), 175.89 (C=O), 177.77 (C=O).

Mass-spectrum 4h: found: *m/z* : 488.3469 $[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m/z*: 488.3403.

**Preparation of 5a.** The synthesis was realized by analogy of 4a-synthesis. Reacting between 0.18 ml (2 mmol) of aniline, 0.30 g (2 mmol) adamantane-2-on, 0.36 g (2 mmol) of adamantane-1-carboxylic acid and 0.23 ml (2 mmol) of ethylisocyanoacetate in 2 ml ethanol, at the room temperature, by the above-described method and chromatography on the $SiO_2$ column (petroleum/ethylacetate, 9/1). 0.47 g (43 %) of yellow oil was obtained. $R_f$ = 0.13 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.27 (3H, t, *J* = 7.2, -OCH$_2$<u>CH$_3$</u>),1.63 - 1.78 (12H, m, H Ad), 1.85 - 1.92 (8H, m, H Ad), 2.04 - 2.19 (10H, m, H Ad), 3.59(2H, s, -N<u>CH$_2$</u>C$_6$H$_5$), 4.20 (2H, q, *J* = 7.2, -O<u>CH$_2$</u>CH$_3$), 4.43 (2H, s, -NH<u>CH$_2$</u>C=O),6.90 (1H, s, NH), 7.21 - 7.29 (1H, m, H Ar), 7.30 - 7.33 (2H, m, H Ar), 7.35 - 7.37 (2H, m, H Ar).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 14.11 (1C, -OCH$_2$<u>CH$_3$</u>), 26.92 (1C Ad), 27.22 (1C Ad), 28.09 (3C Ad), 32.47 (2C Ad), 32.82 (2C Ad), 34.45 (2C Ad), 36.48 (3C Ad), 37.89 (1C Ad), 39.28 (3C Ad), 41.07 (1C Ad), 43.29 (1C, -NH<u>CH$_2$</u>C=O), 46.04 (1C, C$_6$H$_5$<u>CH$_2$</u>N-), 61.31 (1C, -O<u>CH$_2$</u>CH$_3$), 64.87 (1C Ad), 127.60 (1C Ar), 128.25 (1C Ar), 128.32 (2C Ar), 128.65 (1C Ar), 138.65 (1C Ar), 170.21 (C=O), 175.68 (C=O), 177.76 (C=O).

Mass-spectrum 5a: found: *m/z* 532.3393 $[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m/z*: 532.3301.

**Preparation of 5b.** The synthesis was realized by analogy of 4 a-synthesis. Reacting between 0.18 ml (2 mmol) of aniline, 0.30 g (2 mmol) adamantane-2-on, 0.36 g (2 mmol) of adamantane-1-carboxylic acid and 0.23 ml (2 mmol) of ethylisocyanoacetate in 2 ml ethanol, at the room temperature, by the above-described method and chromatography on the $SiO_2$ column (petroleum/ethylacetate, 9/1). 0.47 g (42 %) of yellow oil was obtained. $R_f$ = 0.16 (acetone/$CCl_4$, 1/4).

$^1$H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 1.28 (3H, t, *J* = 7.2, -OCH$_2$<u>CH$_3$</u>), 1.57 - 1.80 (14H, m, H Ad), 1.81 - 2.07 (12H, m, H Ad), 2.07 - 2.38 (2H, m, H Ad), 2.39 - 2.74 (2H, m, H Ad), 4.15 (2H, q, *J* = 7.2, -O<u>CH$_2$</u>CH$_3$), 4.30 (2H, s, -NH<u>CH$_2$</u>C=O), 6.65 - 6.97 (2H, m, H Ar),7.12 - 7.23 (2H, m, H Ar), 7.30 - 7.42 (1H, m, H Ar), 7.68 (1H, s, <u>NH</u>CO).

$^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 14.08 (1C, -OCH$_2$<u>CH$_3$</u>), 26.80 (2C Ad), 26.82 (2C Ad), 27.92 (2C Ad), 32.63 (2C Ad), 34.15 (2C Ad), 34.17 (2C Ad), 36.00 (1C Ad), 36.44 (2C Ad), 38.88 (2C Ad), 39.25 (1C Ad), 41.42 (1C Ad), 46.97 (1C, -NH<u>CH$_2$</u>C=O), 61.41 (1C, -O<u>CH$_2$</u>CH$_3$), 70.97 (1C, -N-<u>C</u> Ad), 128.62 (1C Ar), 128.92 (2C Ar), 129.11 (2C Ar), 131.78 (1C Ar), 160.09 (C=O), 162.33 (C=O), 170.24 (C=O).

Mass-spectrum 5b: found: *m/z* 518.2896 $[M]^+$. $C_{28}H_{36}N_2O_2$. Calculated *m/z*: 518.3145.

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*ორგანული ქიმია*

# ადამანტანის ფრაგმენტის შემცველი ზოგიერთი ახალი დიპეპტიდის სინთეზი უგის რეაქციით იზოციანიდების ბაზაზე

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