PROCEEDINGS OF THE YEREVAN STATE UNIVERSITY

Chemistry and Biology 2020, **54**(3), p. 188–195

Chemistry

SYNTHESIS OF γ-HYDROXY ACID HYDRAZIDES OF A NEW STRUCTURE AND STUDY OF THEIR ANTIOXIDANT PROPERTIES

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On the basis of cyclic esters a method for producing of γ-hydroxybutyric acids hydrazides has been elaborated. The antioxidant properties of hydrazides were researched by the method of competitive reactions and it was established that they have antioxidant activity.

https://doi.org/10.46991/PYSU:B/2020.54.3.188

***Keywords*:** hydrazides of γ-hydroxybutyric acids, cyclic esters, competitive reactions, antioxidant activity.

Introduction. Organic acid derivatives are widely used as starting compounds in preparative organic chemistry, in particular, hydrazides are used to produce various heterocyclic compounds – oxadiazoles [1], 1,2,4-triazoles [2–4], etc. There are also known a number of studies related to the useful properties of hydrazides of various structures. Acetohydrazides of various structures are known to exhibit antitumor activity against cell lines of human prostate carcinoma [5]. Similar properties are shown by hydrazides of substituted benzoic acids [6], and some hydrazide-hydrazones have antimicrobial properties [7].

The few data presented show that studies in the field of various derivatives of carboxylic acids are relevant and urgent.

A literature search has shown that there are no data on γ-hydroxy acid hydrazides. The interest in these compounds can be explained by the fact that the first representative of the homologous series – γ-hydroxybutyric acid (GHB) plays a crucial role in the human central nervous system, and the sodium salt of GHB is widely used in anesthesiology and ophthalmology. Based on the foregoing, it can be assumed that the insertion of the GHB residue into the molecules of a biologically active substance can lead to manifestation of new useful properties for this class of compounds.

Results and Discussion. The lack of data on the hydrazides mentioned can most likely be explained by the absence of a raw material base, since γ-hydroxy acids and their esters are unstable and GHB, even in aqueous solution, is in equilibrium with a cyclic form:

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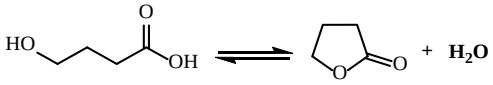
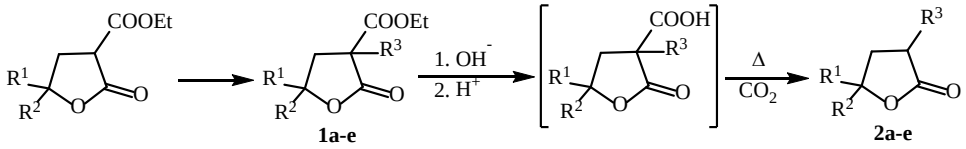


Dihydrofuran-2(3*H*)-one (butyrolactone or butan-4-olide) is a cyclic ester of GHB. Similarly, but under harsher conditions, other representatives of γ-hydroxybutyric acid undergo cyclization to form dihydrofuran-2(3*H*)-ones of various structures [8–10]. Below is a synthesis scheme for a number of compounds from among the dihydrofuran-2(3*H*)-ones mentioned.



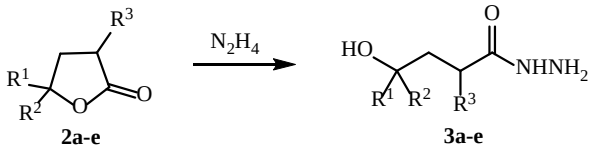
1a-e

1a. R_1 = i-BuOCH$_2$, R_2 = H; R_3 = Bn
1b. R_1 = i-AmOCH$_2$, R_2 = H, R_3 = Bn
1c. R_1 = Am, R_2 = H, R_3 = All
1d. R_1 = R_2 = Me, R_3 = n-Bu
1e. R_1 = Me, R_2 = H, R_3 = i-Am

2a-e

2a. R_1 = i-BuOCH$_2$, R_2 = H; R_3 = Bn
2b. R_1 = i-AmOCH$_2$, R_2 = H, R_3 = Bn
2c. R_1 = Am, R_2 = H, R_3 = All
2d. R_1 = R_2 = Me, R_3 = n-Bu
2e. R_1 = Me, R_2 = H, R_3 = i-Am

Our studies have shown that compounds **2 a**–**e** under mild conditions interact with 85% hydrazine hydrate to form linear γ-hydroxybutyric acid hydrazides (**3 a**–**e**).



2a-e **3a-e**

3a. R_1 = i-BuOCH$_2$, R_2 = H; R_3 = Bn
3b. R_1 = i-AmOCH$_2$, R_2 = H, R_3 = Bn
3c. R_1 = Am, R_2 = H, R_3 = All
3d. R_1 = R_2 = Me, R_3 = n-Bu
3e. R_1 = Me, R_2 = H, R_3 = i-Am

To confirm our assumption about the effect of the γ-hydroxybutane fragment residue on the biological activity of the compounds, the syntheses of new compounds were carried out and it was found that new properties were revealed-hypotensive [11], anti-inflammatory [12], anticonvulsant and hypnosedative [13], antitumor [14] activities. These data once again confirm the expediency of insertion a hydroxypropyl group into the composition of hydrazides **3 a**–**e**.

It is of great interest to study the antioxidant properties of γ-hydroxyacids hydrazides, which makes it possible to increase their use in different fields, especially in medicine. The researches were carried out by a method based on the competitive oxidation of ȮH radicals of a dye in the presence of these substances and without themin an aqueous medium. As a competitive acceptor 4-nitroso-N,N--dimethylaniline (PNDMA) was used, by the rate of discoloration of which the reactivity of OH radicals in relation to compounds **3 a**–**e** was determined.

The rate of ȮH initiation was measured by the rate of change in the optical density of PNDMA in distilled water (**3 a**–**e**). The radicals interact with PNDMA and H_2O_2, resulting in the solution discoloration. The rate of bleaching is the same as the rate of formation of radicals. In the test sample, the bleaching rate decreases due to the competitive interaction of OH radicals.

The reaction can be schematically represented in the following way:

$$H_2O_2 \xrightarrow{h\upsilon} 2\dot{O}H,$$

$$\dot{O}H + PNDMA \xrightarrow{k_{OH}} \text{dye discoloration},$$

$$\dot{O}H + PNDMA \xrightarrow{k_{OH+p}} \text{dye discoloration}.$$

ȮH was initiated by the photolysis of H_2O_2 (10^{-3}*mol/L*) under the influence of UV radiation at $\lambda = 313$ *nm*. To determine the amount of hydrogen peroxides in peroxo solvates, permanganometric method was employed. The UV radiation source was a photolytic equipment with a mercury lamp as a radiation source. Electronic absorption method was used for appropriate measurements.

The kinetic data on the effect of compounds of various concentrations on the optical density of PNDMA depending on the irradiation time are given below (Fig. 1, a–e).

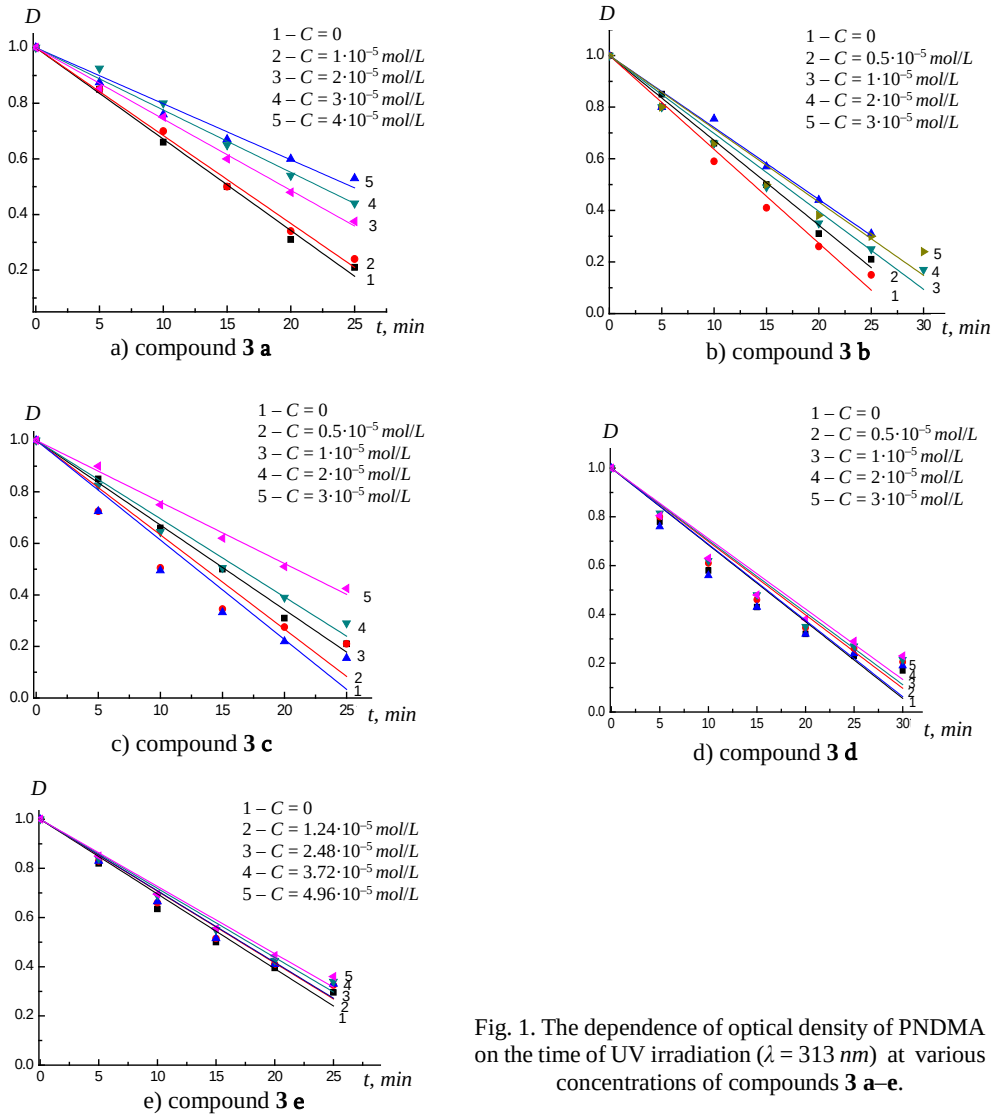


Fig. 1. The dependence of optical density of PNDMA on the time of UV irradiation ($\lambda = 313$ *nm*) at various concentrations of compounds **3 a**–**e**.

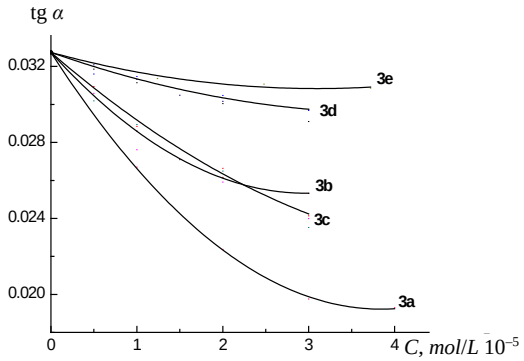


Fig. 2. The dependence of the rate of PNDMA discoloration (in relative units) on concentration.

Based on the experimental data (Fig. 1, a–e) according to [15, 16] the rate constants were calculated by the equation (1):

$$k_{OH+P} = 1.25 \cdot 10^{10}([PNDMA]/[P])\,[(W_1/W_2)^{-1}],\ L \cdot mol^{-1} \cdot s^{-1}, \qquad (1)$$

where $1.25 \cdot 10^{10}$ is the rate constant for the interaction of ȮH radicals with PNDMA, [P] is the concentration of compounds **3 a–e**, W_1 and W_2 are the rates of PNDMA discoloration in distilled water and in the presence of the studied compounds, respectively.

The following data for the reaction rate constant for the interaction of ȮH radicals and the test compounds were obtained.

Compound	Reaction rate constant for the interaction of ȮH radicals + test compound, k, $L \cdot mol^{-1} \cdot s^{-1}$
3 a	$6.20 \cdot 10^8$
3 b	$2.70 \cdot 10^8$
3 c	$4.00 \cdot 10^8$
3 d	$1.71 \cdot 10^8$
3 e	$9.65 \cdot 10^7$
Ascorbic acid (control)	$9.45 \cdot 10^9$

Thus, studies of compounds **3 a–e** have shown that some of them exhibit significant antioxidant activity.

Experimental Part. ^{1}H and ^{13}C NMR spectra were recorded on Varian Mercury-300 MHz in DMSO–CCl_4 mixture (1 : 3). Chemical shifts (δ, *ppm*) are reported as quoted relative to the residual signals of DMSO-d_6 (2.5 for ^{1}H NMR and 39.5 for ^{13}C NMR) as internal references. IR spectra were recorded on a Nicolet 205 (FTIR) spectrophotometer. TLC analysis was performed on Silufol UV-254 plates. All reagents were of reagent grade and were used as such or distilled prior to use. Starting dihydrofuran-2(3*H*)-ones (**2 a–e)** were obtained as previously reported [8–10]. Melting points were determined on "Boetius" micro-heating stage.

2,4,4-Trisubstituted-2-ethoxycarbonyl-4-butanolides (1 a–e). 20 *mL* of absolute ethyl alcohol and 2.3 *g* (0.1 *mol*) of sodium metal were placed in a dry three-necked flask equipped with a stirrer, reflux condenser and dropping funnel. After dissolution

and cooling, 0.1 *mol* of the corresponding 4,4-disubstituted-2-ethoxycarbonyl-butanolide was added dropwise. The mixture was stirred for 15 *min* and 0.11 *mol* of the corresponding halogenide is added dropwise, stirred for 2 *h* without heating and at 75–80°C until neutral reaction of the medium. After distillation of the ethyl alcohol the residue was cooled and acidified (HCl) water was added to pH 2–3; extracted with ether, the extracts were washed with water and dried with anhydrous magnesium sulfate. After distilling off the solvent, the residue was distilled.

*Ethyl 3-benzyl-5-(isobutoxymethyl)-2-oxotetrahydrofuran-3-carboxylate (**1 a**).* Yield 71%, b.p. 160–161°C/1 *Torr*, n_D^{20} 1.5120, d_4^{20} 1.1439. Found, %: C 68.30; H 7.75. $C_{19}H_{26}O_5$. Calculated, %: C 68.24; H 7.84.

*Ethyl 3-benzyl-5-((pentyloxy)methyl)-2-oxotetrahydrofuran-3-carboxylate (**1 b**).* Yield 74%, b.p. 167–168°C/1 *Torr*, n_D^{20} 1.5109, d_4^{20} 1.1175. Found, %: C 68.85; H 8.05. $C_{20}H_{28}O_5$. Calculated, %: C 68.94; H 8.10.

*Ethyl 3-allyl-2-oxo-5-pentyltetrahydrofuran-3-carboxylate (**1 c**).* Yield 89%, b.p. 112–113°C/1 *Torr*, n_D^{20} 1.4675, d_4^{20} 1.0443. Found, %: C 68.85; H 8.05. $C_{15}H_{24}O_4$. Calculated, %: C 67.14; H 9.01.

*Ethyl 3-butyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (**1 d**).* Yield 85%, b.p. 96–97°C/1 *Torr*, n_D^{20} 1.4505, d_4^{20} 1.0258. Found, %: C 64.50; H 9.10. $C_{13}H_{22}O_4$. Calculated, %: C 64.44; H 9.15.

*Ethyl 3-isopentyl-5-methyl-2-oxotetrahydrofuran-3-carboxylate (**1 e**).* Yield 85%, b.p. 99°C/1 *Torr*, n_D^{20} 1.4460, d_4^{20} 1.0210. Found, %: C 64.50; H 9.10. $C_{13}H_{22}O_4$. Calculated, %: C 64.44; H 9.15.

2,4,4-Trisubstituted Butanolides (2 a–e). 0.05 *mol* of the corresponding 2,4,4--trisubstituted-2-ethoxycarbonylbutanolide was added dropwise to a solution of sodium hydroxide 7 *g* (0.175 *mol*) of sodium hydroxide in 16 *mL* of water) and 0.5 *mL* of catamine AB; the whole was stirred for 1 *h* at 20–25°C and 2 *h* at 55–60°C. After cooling, the mixture was acidified with conc. hydrochloric acid to pH 2–3, the product was extracted with ether, washed with water and dried with anhydrous magnesium sulfate. After distilling off the solvent, the residue was subjected to decarboxylation by heating at 150–200°C and pressure of 15–20 *Torr*, the residue was distilled.

*3-Benzyl-5-(isobutoxymethyl)dihydrofuran-2(3H)-one (**2 a**).* Yield 73%, b.p. 141–142°C/1 *Torr*, n_D^{20} 1.5020, d_4^{20} 1.0479. Found, %: C 73.20; H 8.50. $C_{16}H_{22}O_3$. Calculated, %: C 73.25; H 8.45.

*3-Benzyl-5-((isopentyloxy)methyl)dihydrofuran-2(3H)-one (**2 b**).* Yield 75%, b.p. 157–158°C/1 *Torr*, n_D^{20} 1.5009, d_4^{20} 1.0373. Found, %: C 73.95; H 8.70. $C_{17}H_{24}O_3$. Calculated, %: C 73.88; H 8.75.

*3-Allyl-5-pentyldihydrofuran-2(3H)-one (**2 c**).* Yield 91%, b.p. 95–96°C/1 *Torr*, n_D^{20} 1.4580, d_4^{20} 0.9442. Found, %: C 73.50; H 10.20. $C_{12}H_{20}O_2$. Calculated, %: C 73.43; H 10.27.

*3-Butyl-5,5-dimethyldihydrofuran-2(3H)-one (**2 d**).* Yield 80%, b.p. 71–72°C/1 *Torr*, n_D^{20} 1.4400, d_4^{20} 0.9283. Found, %: C 70.50; H 10.60. $C_{10}H_{18}O_2$. Calculated, %: C 70.55; H 10.66.

*3-Isopentyl-5-methyldihydrofuran-2(3H)-one (**2 e**)* Yield 79%, b.p. 72–73°C/1 *Torr*, n_D^{20} 1.4410, d_4^{20} 0.9365. Found, %: C 70.60; H 10.70. $C_{10}H_{18}O_2$. Calculated, %: C 70.55; H 10.66.

Hydrazides of 2,4-disubstituted-4-hydroxypentanoic Acids (3 a–e). A mixture of 0.05 *mol* of 2,4,4-trisubstituted-4-pentanolide, 3 *g* (0.06 *mol*) of 85% hydrazine hydrate in 10 *mL* of ethanol was heated in a boiling water bath for 2 *h* and ethanol was distilled off. The crystalline residue was washed with ether and dried.

The following characteristic absorption bands were observed in the IR spectra of compound **3 a**–**e**, ν, cm^{-1}: 1650 (C=O amide); 1140 (C–O in hydroxyl), 3220–3400 (NH, OH assoc.), δ NH_2 1630.

2-Benzyl-4-hydroxy-5-isobutoxypentanehydrazide (3 a). Yield 87%, m.p. 112°C. ^{1}H NMR (300 *MHz*, DMSO:CCl_4=1:3) δ, *ppm:* 8.61 d (*J* = 7.0 *Hz*, 1H, NH), 7.32–7.05 m ($5H_{arom}$), 4.15 d (*J* = 4.5 *Hz*, 0.5H, OH), 3.98 d (*J* = 5.2 *Hz*, 0.5H, OH), 3.85 br.s (2H, NH_2), 3.65–3.37 m (1H, CHO), 3.29–3.16 m (2H, CH_2O), 3.14 dd (*J* = 6.4; 3.0 *Hz*, 2H, CH_2O), 2.86 ddd (*J* = 19.3; 12.9; 8.3 *Hz*, 1H, CHC=O), 2.72–2.51 m (2H, CH_2Ph), 1.88–1.75 m (1H, $\underline{CH}(CH_3)_2$), 1.71 ddd (0.5H^a, CH$\underline{CH_2}$CH), 1.62–1.52 m (1H^b, CH$\underline{CH_2}$CH), 1.28 ddd (*J* = 13.6; 10.4; 3.2 *Hz*, 0.5H^a, CH$\underline{CH_2}$CH), 0.88 dd (*J* = 6.7; 1.4 *Hz*, 6H, $2CH_3$). ^{13}CNMR (75 *MHz*, DMSO:CCl_4=1:3) δ, *ppm:* 173.9; 173.4; 139.7; 139.6; 137.1; 128.5; 128.5; 127.5; 127.4; 125.2; 125.2; 77.3; 75.3; 74.9; 67.3; 66.6; 42.3; 41.9; 38.6; 37.7; 36.3; 36.2; 27.8; 19.0. Found, %: C 65.30; H 8.85;N 9.60. $C_{16}H_{26}N_2O_3$. Calculated, %: C 65.28; H 8.90; N 9.52.

*2-Benzyl-4-hydroxy-5-(isopentyloxy)pentanehydrazide (**3 b**).* Yield 91%, m.p. 110°C. ^{1}H NMR (300 *MHz*, DMSO:CCl_4=1:3) δ, *ppm:* 8.61 br.s (1H, NHC=O), 7.32–6.99 m ($5H_{arom}$), 3.97 br.d (*J* = 4.7 *Hz*, 1H, OH), 3.82 br.s (2H, NH_2), 3.66–3.50 m (1H, CHO), 3.39 t (*J* = 6.7 *Hz*, 2H, $CH_2\underline{CH_2}O$), 3.22 dd (*J* = 5.4; 2.8 *Hz*, 2H, CH$\underline{CH_2}$O), 3.30–3.09 m (1H, CHC=O), 2.82 dd (*J* = 13.3; 9.0 *Hz*, 1H^a, CH$\underline{CH_2}$CH), 2.64 dd (*J* = 13.3; 5.6 *Hz*, 1Hb, CH$\underline{CH_2}$CH), 1.77–1.64 m (1H, $\underline{CH}(CH_3)_2$), 1.64–1.48 m (2H, $\underline{CH_2}$Ph), 1.48–1.31 m (2H, $\underline{CH_2}CH(CH_3)_2$), 0.90 d (*J* = 6.6 *Hz*, 5H, CH($\underline{CH_3}$)$_2$), 0.87 d (*J* = 6.7 *Hz*, 1H, CH($\underline{CH_3}$)$_2$). ^{13}C NMR (75 *MHz*, DMSO:CCl_4 =1:3) δ, *ppm:*173.9; 139.7; 128.5; 127.4; 125.2; 75.7; 74.9; 74.8; 68.7; 67.3; 42.3; 38.0; 37.7; 36.3; 35.4; 34.3; 25.6; 24.4; 22.3. Found, %: C 66.25; H 9.10; N 9.18. $C_{17}H_{28}N_2O_3$. Calculated, %: C 66.20; H 9.15; N 9.08.

*2-Allyl-4-hydroxynonanehydrazide (**3 c**).* Yield 94%, m.p. 136–137°C. ^{1}H NMR (300 *MHz*, DMSO:CCl_4=1:3) δ, *ppm:* 8.70 s (1H, NH), 5.69 ddt (*J* = 16.8; 10.1; 6.8 *Hz*, 1H, CH=), 5.03–4.94 m (1H^a, =CH_2), 4.94–4.88 m (1H^b, =CH_2), 4.00–3.69 m (3H, NH_2, OH), 3.37 br.s (1H, CHO), 2.37–1.98 m (3H, =CH$\underline{CH_2}$CH), 1.54 ddd (*J* = 15.0; 8.3; 6.8 *Hz*, 1H^a, CH_2), 1.46–1.12 (m, 9H, CH_2), 0.90 (t, *J* = 6.9 *Hz*, 3H, CH_3). ^{13}C NMR (75 *MHz*, DMSO:CCl_4 =1:3) δ, *ppm:* 174.2; 136.1; 115.3; 67.9; 40.3; 39.4; 37.2; 36.0; 31.4; 24.7; 22.1; 13.7. Found, %: C 63.20; H 10.55; N 12.35. $C_{12}H_{24}N_2O_2$. Calculated, %: C 63.12; H 10.59; N 12.27.

*2-(2-Hydroxy-2-methylpropyl)hexanehydrazide (**3 d**).* Yield 86%, m.p. 105–106°C. ^{1}H NMR (300 *MHz*, DMSO:CCl_4=1:3) δ, *ppm:* 8.67 br.s (1H, NHC=O), 3.84 br.s (2H, NH_2), 3.55 br.s (1H, OH), 2.28–2.15 m (1H, CHC=O), 1.84 dd (*J* = 13.9; 9.4 *Hz*, 1H^a, CH_2), 1.57–1.37 m (1H^a, CH_2), 1.36–1.09 m (6H, CH_2), 1.05 d (*J* = 6.3 *Hz*, 6H, C(CH_3)$_2$), 0.89 t (*J* = 7.0 *Hz*, 3H, $CH_2\underline{CH_3}$).^{13}C NMR (75 *MHz*, DMSO:CCl_4= =1:3) δ, *ppm:* 175.4; 68.6; 45.5; 39.3; 33.9; 29.4; 29.1; 28.9; 22.0; 13.6. Found, %: C 59.30; H 11.00; N 13.95. $C_{10}H_{22}N_2O_2$. Calculated, %: C 59.37; H 10.96; N 13.85.

*2-(2-Hydroxy-2-methylpropyl)-5-methylhexanehydrazide (**3 e**).* Yield 80%, m.p. 158–159°C. ^{1}H NMR (300 *MHz*, DMSO:CCl_4=1:3) δ, *ppm:* 8.70 br.s (1H, NHC=O),

3.88 br.s (3H, NH_2, OH), 3.60–3.46 m (1H, CHO), 2.16–2.02 m (1H, CHC=O), 1.70–1.56 m (1H[a], CH_2), 1.56–1.39 m (2H, CH_2), 1.39–1.21 m (2H, CH_2), 1.17–0.96 m (3H, CH_3; 1H[b], CH_2; 1H, $\underline{CH}(CH_3)_2$), 0.87 dd (J = 6.6, 1.9 *Hz*, 6H, $CH(\underline{CH_3})_2$). ^{13}C NMR (75 *MHz*, DMSO:CCl_4 =1:3) *δ, ppm:* 174.6; 64.1; 42.1; 40.9; 35.9; 30.0; 27.5; 23.3; 22.4; 22.1. Found, %: C 59.40; H 10.90; N 13.90. $C_{10}H_{22}N_2O_2$. Calculated, %: C 59.37; H 10.96; N 13.85.

Received 19.06.2020
Reviewed 21.10.2020
Accepted 25.12.2020

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ՆՈՐ ԿԱՌՈՒՑՎԱԾՔԻ γ-ՕՔՍԻԹԹՈՒՆԵՐԻ ՀԻԴՐԱԶԻԴՆԵՐԻ ՍՏԱՑՈՒՄ ԵՎ ԴՐԱՆՑ ՀԱԿԱՕՔՍԻԴԻՉ ՀԱՏԿՈՒԹՅՈՒՆՆԵՐԻ ՀԵՏԱԶՈՏՈՒԹՅՈՒՆ

Մշակվել է γ-օքսիկարագաթթուների հիդրազիդների ստացման եղանակ ցիկլիկ բարդ եթերների հիման վրա: Մրցակցային ռեակցիաների մեթոդով հետազոտվել են հիդրազիդների հակաօքսիդիչ հատկությունները և հաստատվել, որ վերջինները ցուցաբերում են չափավոր հակաօքսիդիչ հատկություններ:

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ПОЛУЧЕНИЕ ГИДРАЗИДОВ γ-ОКСИКИСЛОТ НОВОГО СТРОЕНИЯ И ИССЛЕДОВАНИЕ ИХ АНТИОКСИДАНТНЫХ СВОЙСТВ

На основе циклических сложных эфиров разработан способ получения гидразидов γ-оксимасляных кислот. Методом конкурирующих реакций исследованы антиоксидантные свойства гидразидов и установлено, что последние проявляют умеренную антиоксидантную активность.