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A NEW METHOD FOR THE PREPARATION OF HYDRAZIDES OF SUBSTITUTED GAMMA-HYDROXYBUTANOIC ACIDS

T. V. GHOCHIKYAN [1,2*], A. S. GALSTYAN [1,2**], M. A. SAMVELYAN [1,2***]

[1] *Chemical Research Center, Laboratory of Organic Chemistry, YSU, Armenia*
[2] *Chair of Organic Chemistry, YSU, Armenia*

A method providing a high yield (80–94%) for producing gamma-hydroxybutanoic acids hydrazides by the interaction of various representatives of cyclic esters with 85% hydrazine hydrate has been elaborated. It has been established that the introduction of a gamma-hydroxypropyl residue into the hydrazides composition results in new biological properties.

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***Keywords*:** gamma-hydroxycarboxylic acid hydrazides, cyclic esters.

Introduction. Derivatives of organic acids, particularly hydrazides, are widely used as starting compounds in fine organic chemistry. It has been proven that some derivatives of the naproxen series (S), which are acetohydrazides of various structures, demonstrate antitumor activity against cell lines of human prostate carcinoma [1]. Some hydrazides of substituted benzoic acids also have a similar property [2], a number of hydrazonohydrazides exhibit antioxidant and antimicrobial activity [3]. In addition to the aforesaid, hydrazides of carboxylic acids are successfully used for the synthesis of heterocyclic compounds.

The role of hydrazides in the synthesis of the oxadiazoles and 1,2,4-triazoles is especially important, since numerous representatives of 1,2,4-triazoles, such us Voriconazole, Triazolam, Fluconazole, Itraconazole, Furacilin, Alprazolam, Estazolam and others, are widely used in practical medicine.

The uniqueness of triazoles lies in the fact they are not found in natural raw material, are synthesized and have a wide range of application. The development of new methods for producing 1,2,4-triazolesis is still under way [4–7]. The biological studies show that various 1,2,4-triazoles derivatives possess antimicrobial [8], antitumor [9, 10], antibacterial [11–15], and fungicidal [16, 17] activities. It has been established for the first time that at a certain set of substituents in the molecule, triazole derivatives show affinity for the human adenosine A3 receptor [18] and exhibit insecticidal properties against T cinnabarinus [19]. As can be seen from the

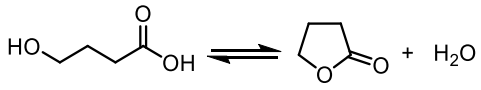
* E-mail: ghochikyan@ysu.am
** E-mail: a_galstyan@ysu.am
*** E-mail: msamvelyan@ysu.am

data presented, studies in the field of various derivatives of 1,2,4-triazoles and their starting compounds are relevant and urgent.

The hydrazides of gamma-hydroxy acid are not described in the literature and there are no data about their studies. The interest in these compounds can be explained by the fact that the first representative of the homologous series – gamma-hydroxybutanoic 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 introduction of a GHB residue into the molecules of the biologically active substance can lead to the manifestation of new useful properties in this class of compounds.

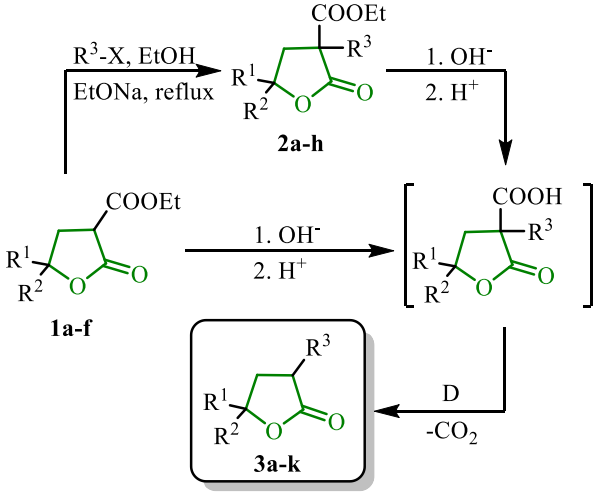
The lack of data on the hydrazides mentioned can most likely be explained by the absence of a raw material base since γ-hydroxy acids and their esters are unstable and GHB even in aqueous solution is in equilibrium with a cyclic form (Scheme 1).



Scheme 1. The equilibrium state of GHB (aq).

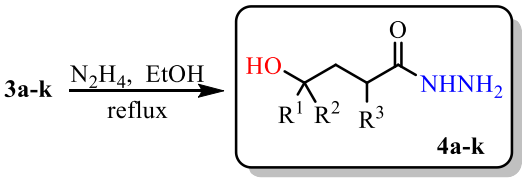
In this study, on the basis of some hydrazides synthesized by us, syntheses of corresponding thiosemicarbazides, 1,2,4-triazoles, were carried out. As a result, it was found that the introduction of a hydroxypropyl group into the composition of the mentioned series reveals new features: hypotensive [20], anti-inflammatory [21], anticonvulsant, hypnotic [22], and antitumor [23] activities. These data once again confirm the expediency of introducing a hydroxylpropyl group into the compositionns.

Results and Discussion. Dihydrofuran-2(3*H*)-one (butyrolactone or butan-4--olide) is a cyclic ester of GHB. Similarly, but under harsher conditions, other representatives of GHB undergo cyclization with the formation of dihydrofuran-2(3*H*)-ones of various structures. We previously synthesized a series of 2,4,4-trisubstituted-4-butanolides according to Scheme 2 (**3a**–**k**) [24–26].



Scheme 2. Synthesis of 2,4,4-trisubstituted-4-butanolides.

Our studies have shown that compounds **3 a**–**k** under mild conditions interacted with 85% hydrazine hydrate to form linear GHB hydrazides (see Scheme 3 and Table) (**4 a**–**k**).



Scheme 3. Synthesis of gamma-hydroxycarboxylic acid hydrazides (**4 a**–**k**)

*Yields of gamma-hydroxycarboxylic acids hydrazides (**4 a**–**k**)*

Compound	R^1	R^2	R^3	Yield, %
4 a	$PrOCH_2$	H	Et	93
4 b	*iso*-$BuOCH_2$	H	H	90
4 c	*iso*-$BuOCH_2$	H	Bu	85
4 d	$AmOCH_2$	H	H	89
4 e	Am	H	H	85
4 f	$PrOCH_2$	H	Bu	83
4 g	*iso*-$BuOCH_2$	H	Bn	87
4 h	*iso*-$AmOCH_2$	H	Bn	91
4 i	Am	H	All	94
4 j	Me	Me	Bu	86
4 k	Me	H	*iso*-Am	80

Experimental Part. The structure of the synthesized compounds was confirmed by ^{1}H and ^{13}C NMR spectra recorded on A Varian Mercury-300 *MHz* NMR spectrometer in DMSO–CCl_4 mixture (1:3), chemical shifts (δ) in *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. The coupling constants (*J*) are given in Hertz. 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 used as such or distilled prior to use. The starting dihydrofuran-2(3*H*)--ones **2 a**–**3 k** were prepared as previously reported [20–21]. Melting points were determined on a Boetius micro-heating stage.

2,4,4–Trisubstituted-2-ethoxycarbonyl-4-butanolides (2 a–h). 20 *mL* of absolute ethyl alcohol and 2.3 *g* (0.1 *mol*) of sodium metal are 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--ethoxycarbonylbutanolide is added dropwise. The mixture is stirred for 15 *min*, and 0.11 *mol* of the corresponding halide is added dropwise, stirred for 2 *h* without heating and at 75–80°C until neutral reaction of the medium. After distillation of ethyl alcohol, the residue is cooled and acidified (HCl) water is added to pH 2–3; extracted with ether, the extracts are washed with water and dried with anhydrous magnesium sulfate. After distilling off the solvent, the residue is distilled.

*Ethyl 3-benzyl-5-(isobutoxymethyl)-2-oxotetrahydrofuran-3-carboxylate (**2a**).* 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 (**2b**).* 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 (**2c**).* 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-ethyl-2-oxo-5-(propoxymethyl)tetrahydrofuran-3-carboxylate (**1d**).* Yield 83%, b.p. 109–111°C/1 *Torr*, n_D^{20} 1.4515, d_4^{20} 1.0245. Found, %: C 60.50; H 8.10. $C_{13}H_{22}O_5$. Calculated, %: C 660.45; H 9.18.

*Ethyl 3-butyl-5-(propoxymethyl)-2-oxotetrahydrofuran-3-carboxylate (**1e**).* Yield 79%, b.p. 115–116°C/1 *Torr*, n_D^{20} 1.4525, d_4^{20} 1.0193. Found, %: C 64.05; H 9.35. $C_{16}H_{28}O_5$. Calculated, %: C 63.97; H 9.45.

*Ethyl 3-butyl-2-oxo-5-(propoxymethyl)-tetrahydrofuran-3-carboxylate (**1f**).* Yield 85%, b.p. 117–118°C/1 *Torr*, n_D^{20} 1.4520, d_4^{20} 1.0200. Found, %: C 63.00; H 9.10. $C_{15}H_{26}O_5$. Calculated, %: C 62.91; H 9.15.

*Ethyl 3-butyl-5,5-dimethyl-2-oxotetrahydrofuran-3-carboxylate (**2g**).* 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 (**2h**).* 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 (3 a–k). 0.05 *mol* of the corresponding 2,4,4-trisubstituted-2-ethoxycarbonylbutanolide is 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 is stirred for 1 *h* at 20–25°C and 2 *h* at 55–60°C. After cooling, the mixture is acidified with concentrated hydrochloric acid to pH 2–3, the product is extracted with ether, washed with water, and dried with anhydrous magnesium sulfate. After distilling off the solvent, the residue is subjected to decarboxylation by heating at 150–200°C and pressure of 15–20 *mm* Hg, the residue is distilled.

*3-Ethyl-5-(propoxymethyl)dihydrofuran-2(3H)-one (**3a**).* Yield 88%, b.p. 94–95°C/1 *Torr*, n_D^{20} 1.4403, d_4^{20} 0.9345. Found, %: C 64.55; H 9.74. $C_{10}H_{18}O_3$. Calculated, %: C 64.49; H 9.74.

*5-(Isobutoxymethyl)dihydrofuran-2(3H)-one (**3b**).* Yield 75%, b.p. 92–93°C/2 *Torr*, n_D^{20} 1.4445, d_4^{20} 1.0151. Found, %: C 62.85; H 9.25. $C_9H_{16}O_3$. Calculated, %:C 62.77; H 9.36.

*3-Butyl-5-(isobutoxymethyl)dihydrofuran-2(3H)-one (**3c**).* Yield 91%, b.p. 100–101°C/1 *Torr*, n_D^{20} 1.4425, d_4^{20} 0.9301. Found, %: C 62.70; H 9.40. $C_9H_{16}O_3$. Calculated, %: C 62.77; H 9.36.

*5-((Pentyloxy)methyl)dihydrofuran-2(3H)-one (**3d**).* Yield 71%, b.p. 98°C/2 *Torr*, n_D^{20} 1.4475, d_4^{20} 1.0075. Found, %: C 64.55; H 9.70. $C_{10}H_{18}O_3$. Calculated, %: C 64.49; H 9.74.

*5-Pentyldihydrofuran-2(3H)-one (**3e**).* Yield 98%, b.p. 81–82°C/1 *Torr*, n_D^{20} 1.4460, d_4^{20} 0.9502. Found, %: C 69.25; H 10.25. $C_9H_{16}O_2$. Calculated, %: C 69.19; H 10.32.

*3-Butyl-5-(propoxymethyl)dihydrofuran-2(3H)-one (**3f**).* Yield 90%, b.p. 105–106°C/1 *Torr*, n_D^{20} 1.4430, d_4^{20} 1.1193. Found, %: C 67.35; H 10.40. $C_{12}H_{22}O_3$. Calculated, %: C 67.26; H 10.35.

*3-Benzyl-5-(isobutoxymethyl)dihydrofuran-2(3H)-one (**3g**).* 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 (**3h**).* 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 (**3i**).* 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 (**3j**).* 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 (**3k**).* Yield 79%, b.p. 72–73°C/2 *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 (4a–k). 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 is heated in a boiling water bath for 2 *h* and ethanol is distilled off. The crystalline residue is washed with ether and dried.

*2-Ethyl-4-hydroxy-5-propoxypentanehydrazide (**4a**).* Yield 93%, m.p. 119–120°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 8.70 s (1H, NHC=O), 3.91 br.s (3H, OH, NH_2), 3.60–3.47 m (1H, CHOH), 3.35 t (*J* = 6.6 *Hz*, 2H, $OCH_2CH_2CH_3$), 3.23 dd (*J* = 5.4 *Hz*, 1.3 *Hz*, 2H, CH_2CHOH), 2.13 dtd (*J* = 8.8 *Hz*, 7.0 *Hz*, 5.3 *Hz*, 1H, CHC=O), 1.62–1.33 m (6H, CH_2), 0.91 t (*J* = 7.4 *Hz*, 3H, CH_3), 0.82 t (*J* = 7.4 *Hz*, 3H,CH_3).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 174.6, 74.9, 72.1, 67.3, 41.9, 36.3, 24.7, 22.4, 11.4, 10.2. Found, %: C 55.10; H 10.10; N 12.90. $C_{10}H_{22}N_2O_3$. Calculated, %: C 55.02; H 10.16; N 12.83.

*4-Hydroxy-5-isobutoxypentanehydrazide (**4b**).* Yield 90%, m.p. 65–66°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 9.62 s (0.4H, NHC=O), 8.77 s (0.6H, NHC=O), 4.25 dd (*J* = 11.9 *Hz*, 4.8 *Hz*, 1H, OH), 3.90 s (2H, NH_2), 3.71–3.42 m (1H, CHO), 3.33–3.06 m (4H, OCH_2), 2.38–2.03 m (2H, CH_2C=O), 1.97–1.64 m (2H, CH_2), 1.59–1.32 m (1H, CH), 0.89 d (*J* = 6.7 *Hz*, 6H, $CH(CH_3)_2$).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3) *δ*: 172.1, 170.7, 77.4, 75.0, 68.5, 68.3, 29.7, 29.4, 29.3, 27.9, 19.1. Found, %: C 53.00; H 9.80; N 13.80. $C_9H_{20}N_2O_3$. Calculated, %: C 52.92; H 9.87; N 13.71.

*2-(2-Hydroxy-3-isobutoxypropyl)hexanehydrazide (**4c**).* Yield 85%, m.p. 126–127°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 8.67 s (1H, NHC=O), 3.86 br.s (3H, OH, NH_2), 3.64–3.43 m (1H, CHOH), 3.29–3.18 m (2H, OCH_2CHO), 3.16 d (*J* = 6.6 *Hz*, 2H, OCH_2CHMe_2), 2.19 dtd (*J* = 9.4 *Hz*, 6.9 *Hz*, 4.8 *Hz*, 1H, CHC=O), 1.91–1.75 m (1H, $CHMe_2$), 1.57–1.41 m (3H, CH_2), 1.40–1.25 m (3H, CH_2), 1.24–1.10 m (2H, CH_2), 0.95–0.84 d (*J* = 6.6 *Hz*, 6H, $CH(CH_3)_2$), 0.83–0.81 d (*J* = 7.3 *Hz*, 3H, CH_2CH_3).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), δ: 174.7, 77.3, 75.0, 67.3, 40.3, 36.6, 31.5, 28.9, 27.8, 22.1, 19.9, 13.6. Found, %: C 60.05; H 10.75; N 10.85. $C_{13}H_{28}N_2O_3$. Calculated, %: C 59.97; H 10.84; N 10.76.

*4-Hydroxy-5-(pentyloxy)pentanehydrazide (**4d**).* Yield 89%, m.p. 71–72°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), δ: 9.62 br.s (0.15H, NHC=O), 8.77 br.s (0.8H, NHC=O), 4.26 d (*J* = 4.7 *Hz*, 0.8H, OH), 4.22 d (*J* = 4.9 *Hz*, 0.15H, OH), 3.89 br.s (2H, NH_2), 3.65–3.46 m (1H, CHO), 3.38 t (*J* = 6.6 *Hz*, 2H, $CH_2\underline{CH_2}O$), 3.26 dd (*J* = 9.5 *Hz*, 5.8 *Hz*, 1H^a, $CH\underline{CH_2}O$), 3.19 dd (*J* = 9.5 *Hz*, 5.6 *Hz*, 1H^b, $CH\underline{CH_2}O$), 2.30–2.05 m (2H, $CH_2\underline{CH_2}C{=}O$), 1.73 dddd (*J* = 13.8 *Hz*, 8.0 *Hz*, 7.3 *Hz*, 3.5 *Hz*, 1H^a, $\underline{CH_2}CH_2C{=}O$), 1.59–1.42 m (2H, $\underline{CH_2}CH_2O$, 1H^b, $\underline{CH_2}CH_2C{=}O$), 1.39–1.24 m (4H, $\underline{CH_2CH_2}CH_3$), 0.97–0.85 m (3H, CH_3).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), δ: 172.1, 170.8, 74.8, 70.5, 68.5, 68.3, 29.7, 29.4, 28.9, 27.8, 22.0, 13.7. Found, %: C 55.05; H 10.10; N 12.85. $C_{10}H_{22}N_2O_3$. Calculated, %: C 55.02; H 10.16; N 12.83.

*4-Hydroxynonanehydrazide (**4e**).* Yield 85%, m.p. 81–82°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), δ: 9.60 br.s (0.25H, NHC=O), 8.74 br.s (0.75H, NHC=O), 4.18–3.98 m (1H, OH), 3.88 br.s (2H, NH_2), 3.53–3.20 m (1H, CHO), 2.32–2.05 m (2H, $CH_2C{=}O$), 1.75–1.57 m (1H^a, CH_2), 1.57–1.12 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:172.2, 170.7, 69.3, 69.1, 37.1, 32.7, 32.7, 31.5, 30.0, 29.7, 24.9, 22.1, 13.7. Found, %: C57.45; H 10.65; N 14.95. $C_9H_{20}N_2O_2$. Calculated, %: C 57.42; H 10.71; N 14.88.

*2-(2-hydroxy-3-propoxypropyl)hexanehydrazide (**4f**).* Yield 83%, m.p. 122–123°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), δ: 8.68 s (1H, NHC=O), 3.89 br.s (3H, OH, NH_2), 3.61–3.47 m (1H, $\underline{CH}OH$), 3.35 t (*J* = 6.6 *Hz*, 2H, OCH_2CH_2), 3.23 m (2H, OCH_2CHOH), 2.18 dtd (*J* = 9.4 *Hz*, 7.0 *Hz*, 4.9 *Hz*, 1H, CHC=O), 1.65–1.44 m (5H, CH_2), 1.42–1.24 m (3H, CH_2), 1.24–1.12 m (2H, CH_2), 0.96–0.85 m (6H, CH_3).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), δ:174.7, 87.2, 74.8, 72.0, 67.3, 40.3, 36.7, 31.5, 28.9, 22.3, 22.1, 13.6, 10.2. Found, %: C 58.51; H 10.64; N 11.37. $C_{12}H_{26}N_2O_3$. Calculated, %: C 58.61; H 10.60; N 11.49.

*2-Benzyl-4-hydroxy-5-isobutoxypentanehydrazide (**4g**).* Yield 87%, m.p.112°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), δ: 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 *Hz*, 3.0 *Hz*, 2H, CH_2O), 2.86 ddd (*J* = 19.3 *Hz*, 12.9 *Hz*, 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 *Hz*, 10.4 *Hz*, 3.2 *Hz*, 0.5H^a, $CH\underline{CH_2}CH$), 0.88 (dd, *J* = 6.7, 1.4 *Hz*, 6H, $2CH_3$).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), δ: 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 (**4h**).* Yield 91%, m.p. 110°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), δ: 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 *Hz*,

2.8 *Hz*, 2H, CH<u>CH$_2$</u>O), 3.30–3.09 m (1H, CHC=O), 2.82 dd (*J* = 13.3 *Hz*, 9.0 *Hz*, 1H^a, CH<u>CH$_2$</u>CH), 2.64 dd (*J* = 13.3 *Hz*, 5.6 *Hz*, 1Hb, CH<u>CH$_2$</u>CH), 1.77–1.64 m (1H, <u>CH</u>(CH$_3$)$_2$), 1.64–1.48 m (2H, <u>CH$_2$</u>Ph), 1.48–1.31 m (2H, <u>CH$_2$</u>CH(CH$_3$)$_2$), 0.90 d (*J* = 6.6 *Hz*, 5H, CH(<u>CH$_3$</u>)$_2$), 0.87 d (*J* = 6.7 *Hz*, 1H, CH(<u>CH$_3$</u>)$_2$).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 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 (**4i**).* Yield 94%, m.p. 136–137°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 8.70 s (1H, NH), 5.69 ddt (*J* = 16.8 *Hz*, 10.1 *Hz*, 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, NH2, OH), 3.37 br.s (1H, CHO), 2.37–1.98 m (3H, =CH<u>CH$_2$CH</u>), 1.54 ddd (*J* = 15.0 *Hz*, 8.3 *Hz*, 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*: 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 (**4j**).* Yield 86%, m.p. 105–106°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 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 *Hz*, 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$_2$<u>CH$_3$</u>).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 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 (**4k**).* Yield 80%, m.p. 158–159°C. ^{1}H NMR (300 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 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, <u>CH</u>(CH$_3$)$_2$), 0.87 dd (*J* = 6.6 *Hz*, 1.9 *Hz*, 6H, CH(<u>CH$_3$</u>)$_2$).

^{13}C NMR (75 *MHz*, DMSO/CCl_4 = 1/3), *δ*: 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.

Conclusion. The interaction of various representatives of cyclic ester with 85% hydrazine hydrates leads to the production of gamma-hydroxybutanoic acid with a high yield (80–94%).

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Տ. Վ. ՂՈՉԻԿՅԱՆ, Ա. Ս.ԳԱԼՍՏՅԱՆ, Մ. Ա. ՍԱՄՎԵԼՅԱՆ

ՏԵՂԱԿԱԼՎԱԾ ԳԱՄԱ-ՀԻԴՐՕՔՍԻԲՈՒՏԱՆԱԹԹՈՒՆԵՐԻ ՀԻԴՐԱԶԻԴՆԵՐԻ ՍԻՆԹԵԶԻ ՆՈՐ ՄԵԹՈԴ

Մշակվել է գամա-հիդրօքսիբուտանաթթուների հիդրազիդների ստացման նոր մեթոդ՝ տարբեր կառուցվածքի ցիկլիկ էսթերների և 85%-անոց հիդրազին հիդրատի փոխազդեցությամբ: Ցույց է տրվել, որ հիդրազիդների կառուցվածքում գամա-հիդրօքսիպրոպիլ տեղակալիչի ներմուծումը կարող է հանգեցնել նոր, կենսաբանորեն ակտիվ միացությունների:

Т. В. КОЧИКЯН, А. С. ГАЛСТЯН, М. А. САМВЕЛЯН

НОВЫЙ МЕТОД ПОЛУЧЕНИЯ ГИДРАЗИДОВ ЗАМЕЩЕННЫХ ГАММА-ГИДРОКСИБУТАНОВЫХ КИСЛОТ

Разработан новый метод получения гидразидов γ-гидроксибутановых кислот взаимодействием различных представителей циклических эфиров с 85%-м гидразингидратом. Показано, что введение в структуру гидразидов гамма-гидроксипропильного заместителя может привести к новым биологически активным соединениям.