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# Amides Of Ricinoleic, Lactic, Sorbic, Cinnamic And Itaconic Acids Based On Homoveratrylamine

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***Annotation: Amides of ricinoleic, lactic, cinnamic, sorbic, itaconic acids with homoveratrylamine have been synthesized in 70-88% yields. The structure of the obtained compounds was confirmed by the data of NMR spectroscopy and gas chromatography-mass spectrometry.***

***Keywords: homoveratrylamine, synthesis, acids, amides, NMR spectroscopy.***

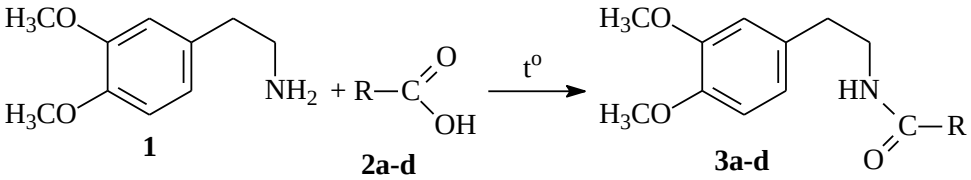
According to the world literature amides are widely used in the creation of drugs, such as primary (vitamin PP, piracetam), secondary (paracetamol, folic acid, lidocaine, novocainamide, barbiturates, number of antibiotics of the penicillin group, cephalosporins, chloramphenicol, benzodiazepine derivatives ), tertiary (analgesics - amidopyrine, analgin, butadione, etc.) amides are important and demanded drugs [1]. The development of various kinds of activity by amides is due to the presence of several functional groups, including the amide group.

One-step conversion of carboxylic acids [2] and esters into amides can also be carried out using various reagents and in the presence of catalysts [3-7]. The preparation of these reagents is a multi-step process. Therefore, the development of a simple and selective method for the preparation of amides and the creation of new biological active compounds on its basis is a necessary task.

Consequently, the study of condensation reaction of acids with homoveratrylamine is an urgent task, since the amides obtained in this case are potentially active BACs, as well as accesseble and convenient intermediates in synthesis of nitrogen-containing heterocycles.

In previous reports [8-10] it was shown that the formation of amides based on homoveratrylamine and a number of acids depends on its structure and the number of carbon atoms of the acids. Thus, during the condensation of homoveratrylamine with dibasic fatty acids from C5 to C10, mainly target amides are formed [11], while with succinic acid (C4), a mixture of two substances, amide and imide, is obtained [10]. A specific feature of the condensation of homoveratrylamine with malic and fumaric acids is the production of three products: β-lactam, amide, and imide [12].

Continuing our previous work [11], we carried out condensation reaction of homoveratrylamine (1) with carboxylic acids (2a-d).

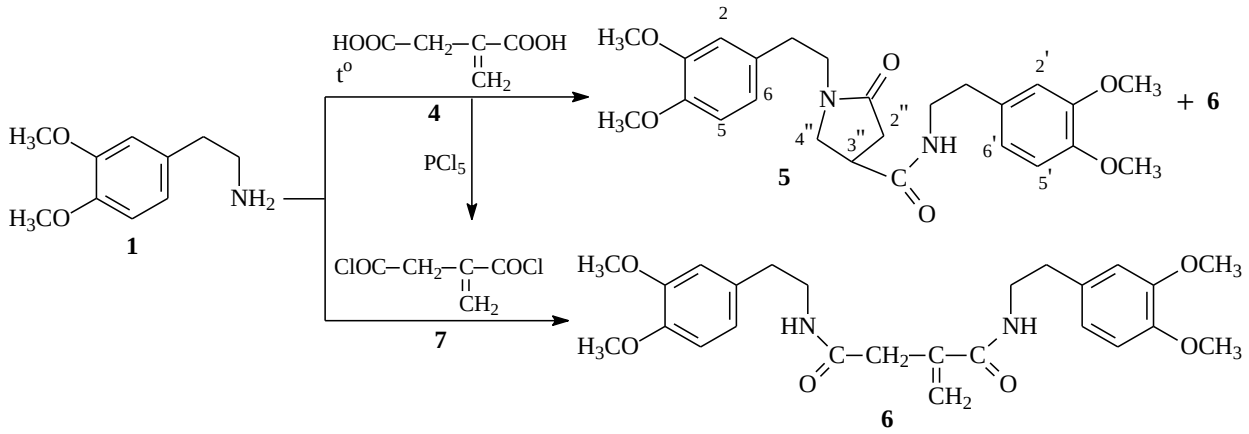


**1** **2a-d** **3a-d**

**a.** $CH_3-(CH_2)_5-CH(OH)-CH_2-CH=CH-(CH_2)_7-$ ; **c.** $C_6H_5-CH=CH-$;

**b.** $CH_3-CH(OH)-$; **d.** $CH_3-CH=CH-CH=CH-$;

The reactions with ricinoleic (2a), lactic (2b), cinnamic (2c), and sorbic (2d) acids proceeded with the formation of target amides 3a-d in 70-86% yields. Whereas heating **1** with itaconic acid (**4**) led to the formation of N, 1-bis (3,4-dimethoxyphenylethyl)-2-oxopyrrolidine-3-carboxyamide **5** (88%) and **6** (6%). Diamide **6** was prepared in 60% yield using itaconic acid dichloroanhydride.



**1** **4** **5** **6** **7**

Due to the double bond location in the itaconic acid molecule, it is considered active in relation to its isomers (citraconic and mesoconic acids). Because of the high density of the electron pair in the double bond of acid molecule and its redistribution, the probability of the formation of a cyclic product in the presence of homoveratrylamine increases. When the reaction mixture is heated to 180°C, product 5 is formed due to breaking of the double bond, and at room temperature in the presence of itaconic acid dichloride, product 6 is mainly formed.

The structure of the synthesized amides was established based on the data of mass spectra and $^1H$ and $C^{13}$ NMR. In the mass spectrum of all amides, the characteristic peak is the peak of the molecular ion m / z M +. In the $^1H$ NMR spectrum of all amides, the signals from aromatic protons of 1,3,4 - substituted β-phenylethylamine appear in the 6.65 - 6.77 ppm range. The H-5 proton is observed at 6.73 (3a), 6.76 ppm (3b and 3c), 6.70 (5) in the form of a doublet with CSCR J = 8.0 - 8.6 Hz. The H-6 protons of the aromatic ring resonate as doublet of the doublets at 6.69 ppm. (J = 1.6-2.0 Hz and 8.0 - 8.6 Hz), and H-2 - at 6.70 ppm. (doublet with J = 1.6-2.0 Hz). In compounds 3a and 5, these signals are overlapped. The signals from the β-methylene group (-CH2-) appear as a two-proton quartet (for 3a at 3.42 ppm J = 6.7; for 3b at 4.17 ppm; for 3d, one-proton quartets at 3.94, 4.11 ppm) or multiplet (3b, 3.57 ppm), the α-methylene group resonates in a stronger field as a two-proton triplet at

2.68-278 ppm. with CSCR J = 6.9 Hz. The signals of remaining protons appear in the area corresponding to the obtained structure.

In NMR $H^1$ spectrum of 5 there is a signal from one NH group at 6.25 ppm. and there is no signal for = CH2 group. In the area 2.6-3.6 ppm substance 5 along with α-,β- protons, protons of the 2 " - methylene group of the oxopyrrolidine ring appear at 2.58 ppm. in the form of a multiplet, methine proton H-3 " at 2.96 ppm and protons 4 " of the methylene group at 3.33 (H-ax) and 3.56 ppm. (H-eq).

All these data confirm the formula 5 given for itaconic acid monoamide.

According to the PASS data, the obtained compounds should have a cytoprotective effect.

*Experimental part:*

NMR $H^1$ and $C^{13}$ spectra were recorded on Unity-400 + Varian (400 MHz) (solvent $CDCl_3$, internal standard HMDS). High-resolution mass spectra were recorded on an Agilent Technologies 6420 Triple Quad LC/MS instrument. The Rf value was determined on silica gel plates LS 5/40 (Czechoslovakia) using a solvent system chloroform: methanol 1 (8: 1), 2 (8: 2). Melting points of all synthesized substances were determined on a Stuart SMP10 Melting Point Apparatus. Itaconic acid dichloride was prepared according to the method [13].

*General procedure for the preparation of amides 3a-g.*

A mixture of 1 mole of homoveratrylamine and 1 mole of carboxylic acid was dissolved in 5 ml of methanol. Spontaneous heating occurred. The mixture was then heated in an oil bath for 2 h at 180 ° C. The progress of the reaction was monitored by TLC.The reaction mixture was dissolved in 100 ml of chloroform.The chloroform layer was first washed with 3% hydrochloric acid solution and with water until neutral. Following, the chloroform solution was washed with a 2% sodium hydroxide solution and with water until neutral.Obtained chloroform was dried over Na2SO4 and evaporated. The residue was crystallized from acetone-hexane mixture.

**(Z) -N- (3,4-Dimethoxyphenylethyl) -12-hydroxyoctadeken-9-amide (cis) (3a), $C_{28}H_{47}O_4N$** has been prepared from 1.65 g (0.0091 mol) of homoveratrylamine and 2.72 g (0.0091 mol) of ricinoleic acid. The yield is 3.62 g (86%), mp. 88-90 ° C (acetone-hexane), Rf 0.83 (system 1).

$^1$H NMR spectrum (400 MHz, $CDCl_3$, ppm, J / Hz): 0.80 (3H, t, J = 7.0, H-18′), 1.17 (22H, m, H-2′-7′, H -13′-17′), 1.51 (2H, t, J = 7.1, H-8′), 1.93 (1H, q, J = 6.0, H-12′), 2.04 (2H, t, J = 7.7, H-11′), 2.68 (2H, t, J = 6.9, H-α), 3.42 (2H, q, J = 6.7, H-β), 3.79 (6H, s, $OCH_3$) , 5.26 (2H, br.t, J = 6.3, H-9′, 10′), and 5.43 (1H, br.s, OH-12′), 6.65 (2H, m, H-2, 6), 6.73 (1H, d, J = 8.6, H-5).

$^{13}$C NMR spectrum (100 MHz, $CDCl_3$), ppm (J / Hz): 14.20 (C-18′), 22.76 (C-17′), 25.76 (C-14′), 25.85 (C-3′ ), 27.25 (C-4′), 27.29 (C-5′), 29.21 (C-6′), 29.35 (C-15′), 29.39 (C-7′), 29.58 (C-8′), 29.78 (C-16′), 29.83 (C-12′), 31.97 (C-2′), 35.38 (C-13′), 35.80 (C-11′), 36.92 (C-α), 40.70 (C -β), 173.27 (C-1′), 55.91 (C-$OCH_3$), 55.97 (C-$OCH_3$), 111.35 (C-5), 111.92 (C-2), 120.69 (C-6), 129.78 (C -10′), 130.07 (C-9′), 131.49 (C-1), 147.72 (C-4), 149.08 (C-3), 173.27 (C-1′).

Mass spectrum m / z 461$M^+$ (462), 448, 434, 420, 124, 60.

N- (3,4-Dimethoxyphenylethyl)-2-hydroxypropanamide (3b), **$C_{13}H_{19}O_4N$**. has been prepared from 1.81 g (0.01 mol) of homoveratrylamine and 0.9 g (0.01 mol) and lactic acid. The yield is 1.77 g (70%), mp. 70-71 ° C (acetone - hexane), $R_f$ 0.40 (system 2).

$^1$H NMR spectrum (400 MHz, $CDCl_3$, ppm, J / Hz): 1.34 (3H, d, J = 6.7, H-3′), 2.73 (2H, t, J = 7.1, H-α), 3.46 (2H, q, J = 6.7, H-β), 3.81 (3H, s, $OCH_3$), 3.82 (3H, s, $OCH_3$), 4.10

(1H, br.s, OH), 4.17 (1H, q, J = 6.8, H-2′), 6.69 (2H, overlapped, H = 2, 6), 6.77 (1H, d, J = 8.6, H-5), 6.90 (1H, br.s, NH).

$^{13}$C NMR spectrum (100 MHz, $CDCl_3$), ppm (J, Hz): 21.26 (C-3′), 35.19 (C-α), 40.60 (C-β), 55.98 (C-$OCH_3$), 55.98 (C-$OCH_3$, 68.10 (C-2′), 111.44 (C-5), 111.97 (C-2), 120.73 (C-6), 131.10 (C-1), 147.73 (C-4), 149.01 (C-3), 175.56 (C-1′).

Macc spectrum m / z: 253 $[M]^+$, 224, 165, 124, 60.

**N- (3,4-Dimethoxyphenylethyl) -3-phenylpronenamide (3c), $C_{19}H_{21}O_3N$** has been prepared from 2.0 g (0.011 mol) of homoveratrylamine and 1.64 (0.011 mol) of cinnamic acid. The yield is 2.78 g (81%), mp 121-122 ° C (acetone), $R_f$ 0.82 (system 2).

$^1$H NMR spectrum (400 MHz, $CDCl_3$, ppm, J / Hz): 2.78 (2H, t, J = 6.9, H-α), 3.57 (2H, br.s, H-β), 3.78 (3H , s, $OCH_3$), 3.79 (3H, s, $OCH_3$), 6.20 (1H, br.s, NH), 6.36 (1H, d, J = 15.6, H-2′), 6.68 (2H, overlapped, H- 2, 6), 6.73 (1H, d, J = 8.0, H-5), 7.27 (3H, m, H-3", 4", 5"), 7.39 (1H, overlapped, H- 2", 6"), 7.59 (1H, d, J = 15.6, H-3′).

$^{13}$C NMR spectrum (100 MHz, $CDCl_3$), ppm (J, Hz): 35.20 (C-α), 41.31 (C-β), 55.96 (C-$OCH_3$), 55.96 (C-$OCH_3$), 111.44 ( C-5), 112.02 (C-2), 120.12 (C-2′), 120.74 (C-6), 127.96 (C-4"), 128.92 (C-2", 6"), 129.96 (C- 3", 5"), 131.29 (C-1), 134.70 (C-1"), 141.73 (C-3′), 147.73 (C-4), 149.11 (C-3), 166.41 (C-1′ ).

Mass spectrum m / z: 311 $M^+$ (312) 219, 165, 113, 60.

N- (3,4-Dimethoxyphenylethyl) -hexa-2,4-dienamide (3d), **$C_{16}H_{21}O_3N$** has been prepared from 1.81 g (0.01 mol) of homoveratrylamine and 1.12 g (0.01 mol) of sorbic acid. The yield is 2.25 g of oily product (82%), $R_f$ 0.71 (system 2).

$^1$H NMR spectrum (400 MHz, $CDCl_3$, ppm, J / Hz): 1.07 (3H, d, J = 6.5, $CH_3$-6′), 2.78 (2H, m, H-α), 3.78 (3H, s, $OCH_3$), 3.79 (3H, s, $OCH_3$), 3.94 and 4.14 (each 1H, m, H-β), 4.63 (1H, br.s, NH), 5.62 (1H, m, H-5′) , 5.90 (1H, d, J = 9.7, H-2′), 6.35 (1H, m, H-4′), 6.70 (4H, overlapped, H-2, 5, 6, 3′).

$^{13}$C NMR spectrum (100 MHz, $CDCl_3$), ppm (J, Hz): 18.03 (C-6′), 35.18 (C-α), 41.15 (C-β), 55.91 (C-$OCH_3$), 55.91 (C-$OCH_3$), 111.23 (C-5), 112.13 (C-2), 120.61 (C-2′), 120.81 (C-6), 124.56 (C-4′), 127.68 (C-5′) , 131.81 (C-1), 137.64 (C-3′), 147.54 (C-4), 148.81 (C-3), 163.69 (C-1′).

N, 1-bis- (3,4-dimethoxyphenylethyl) -2-oxopyrrolidine-3-carboxyamide (5), **$C_{25}H_{32}O_6N_2$** has been prepared from 3.62 g (0.02 mol) of homoveratrylamine and 1.3 g (0.01 mol) of itaconic acid. The yield is 4.0 g (88%) mp 87-88 ° C (acetone - hexane), $R_f$ 0.73 (system 2).

$^1$H NMR spectrum (400 MHz, $CDCl_3$, ppm, J / Hz): 2.58 (2H, m, H-2′′), 2.68 (4H, q, J = 7.8, H-α, α′), 2.96 (1H, n, J = 7.7, H-3′′), 3.33 (1H, t, J = 9.4, H-4′′), 3.42 (4H, q. J = 7.7, H-β, β′), 3.56 (1H, dd, J = 6.8, 9.6, H-4′′), 3.75, 3.76, 3.77, 3.78 (each 3H, s. $OCH_3$-3, 4, 3′, 4′), 6.25 (1H, br., NH), 6.64-6.70 (4H, signals overlapped, H = 2, 2′, 6, 6′), (2H, d, J = 8.5, H-5, 5′).

$^{13}$C NMR spectrum (100 MHz, $CDCl_3$), ppm (J, Hz): 33.05 (C-3′), 35.12 (C- α, α′), 37.47 (C-2′), 41.08 (C- 4′), 44.66 (C-β), 50.58 (C-β′), 56.97 (C-$OCH_3$), 55.97 (C-$OCH_3$), 55.97 (C-$OCH_3$), 55.97 (C-$OCH_3$), 111.40 (C -5, 5′), 111.82 (C-2), 111.92 (C-2′), 120.64 (C-6), 120.71 (C-6′), 130.62 (C-1), 131.12 (C-1′ ), 147.76 (C-4), 147.78 (C-4′), 149.04 (C-4), 149.07 (C-4′), 171.76 (C-1′), 173.56 (C-3a).

Mass spectrum m / z 456 $M^+$, 346, 219, 165, 113, 60.

**$N^1$,$N^4$**-bis (3,4-dimethoxyphenylethyl) -2-methylene succinamide (6), **$C_{25}H_{32}O_6N_2$**. 3 g (0.018 mol) of itaconic acid dichloride was dissolved in 20 ml of benzene. To this solution, 6.5 g (0.036 mol) of homoveratrylamine in 10 ml of benzene was added dropwise over 2

hours while stirring on a magnetic stirrer at room temperature. The progress of the reaction was monitored by TLC. Stirring was continued for another 4 hours and left overnight. Chloroform was added to the reaction mixture. Afterwards, the chloroform solution was washed with a 2% sodium hydroxide solution and water until neutral. The obtained solution was dried over $Na_2SO_4$ and evaporated. The residue was crystallized from acetone. The yield is 60% (4.5 g), mp. 113-114 ° C, $R_f$0.71 (system 1).

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