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Synthesis of Macroheterocycles with Nitrogen−Containing and Ester Fragments from Undecylenic Acid

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Synthesis of three potentially biologically active 34- and 36-membered macroheterocycles with nitrogen-containing and ester fragments using undecylenic acid is developed. It was based on [1+1] condensation of the intermediate oxybis(ethane-2,1-diyl)bis(10-oxoundecanoate) with full dihydrazides of malonic, glutaric or 2,6-pyridinedicarboxylic acids. The structure of the obtained compounds is confirmed by IR and NMR spectroscopy and mass spectrometry.

Keywords: Undecylenic acid, diethylene glycol, dihydrazides, malonic acid, glutaric acid, 2,6- pyridinedicarboxylic acid, nitrogen-containing macroheterocycles, ester fragments, [1+1]- and [2+1]- condensation.

Ундециленовая кислота в синтезе макрогетероциклов с азотсодержащими и эфирными фрагментами

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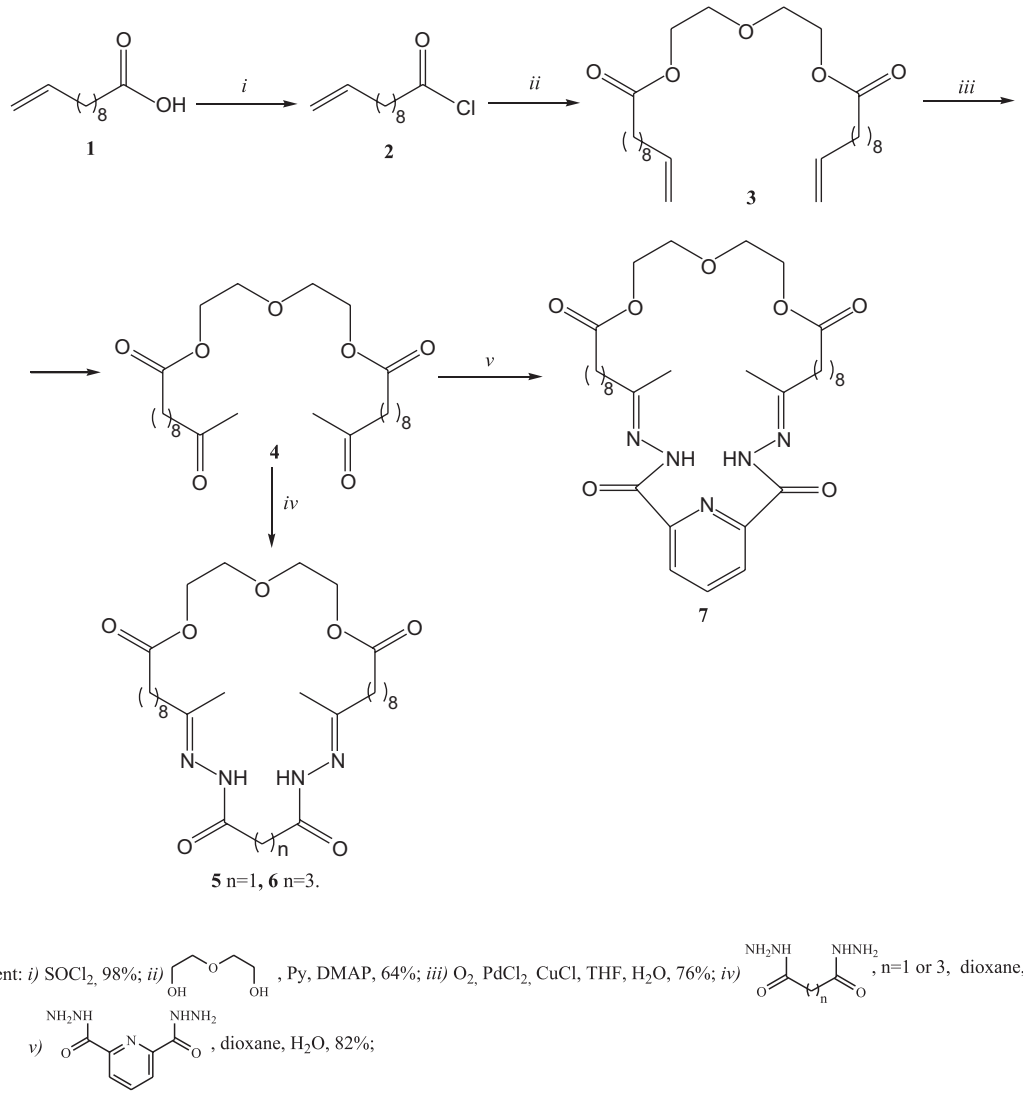
Исходя из ундециленовой кислоты разработан синтез трех потенциально биологически активных 34- и 36-членных макрогетероциклов, с азотсодержащими и эфирными фрагментами на основе [1+1]-конденсации промежуточного дикетодиэфира (оксибис(этан-2,1-диил)бис(10-оксоундеканоат)) с дигидразидами малоновой, глутаровой или 2,6-пиридиндикарбоновой кислот. Структура полученных соединений подтверждена с помощью ИК и ЯМР спектроскопии и масс-спектрометрии.

Ключевые слова: Ундециленовая кислота, диэтиленгликоль, дигидразиды, малоновая кислота, глутаровая кислота, 2,6-пиридиндикарбоновая кислота, макрогетероциклы с азотсодержащими фрагментами, сложноэфирные фрагменты, [1+1]- и [2+1]- конденсации.

For the first time from commercially available product of the destructive distillation of castor oil – undecylenic acid (**1**), which is widely used in directed organic synthesis,[1] in medicine as a fungicidal drug, in cosmetics as fragrances and emollient component,[2] the synthesis of pharmaceutically promising multifunctional 34- and 36-membered macroheterocycles containing oxa-, carboxyl and hydrazide groups was carried out. To do this, undecylenic acid (**1**) was converted to the corresponding acid chloride (**2**), [2+1]-condensation of which with diethylene glycol gave functionalized α,ω-dialkene (**3**). This α,ω-dialkene (**3**) was oxidized by Wakker-Tsuji to the key synthon – diketodiester (**4**). Subsequent [1+1] condensation of the latter with dihydrazides of malonic and glutaric acids for the synthesis of macrolides (**5**) and (**6**) was performed at room temperature and high dilution in 1,4-dioxane (molar ratio substrate:reagent:solvent – 1:1:100). [1+1]-Condensation of diketodiester (**4**) with a hydrazide of 2,6-pyridinedicarboxylic acid in the synthesis of macroheterocycle (**7**) was carried out under the same conditions with the addition



Reagent: *i)* $SOCl_2$, 98%; *ii)* , Py, DMAP, 64%; *iii)* O_2, $PdCl_2$, CuCl, THF, H_2O, 76%; *iv)* , n=1 or 3, dioxane, 86% or 94%.

v) , dioxane, H_2O, 82%;

of 10 eq. of water because of poor solubility of the hydrazide reagent.

Experimental

Analyzes were performed on the equipment at the Center for the Collective Use "Chemistry" of the Ufa Institute of Chemistry of the Russian Academy of Sciences. IR spectra were recorded on the device IR Prestige-21 Shimadzu **(**Fourier Transform Spectrophotometer – Shimadzu) in thin layer. NMR spectra were recorded in $CDCl_3$ and D_2O with TMS internal standard on a Bruker AM-500 spectrometer (operating frequency 500.13 MHz for ^1H; 126.76 MHz for ^{13}C). Mass spectra were recorded on a LC/MS 2010 EV Shimadzu instrument (syringe input, sample solution in CH_3CN at flow rate 60 μL/min) using electrospray ionization (ESI) method with a simultaneous recording of positive and negative ions at capillary potentials 4.5 and –3.5 kV, respectively. The temperature of the capillary interface was 200 °C; the flow of a nebulizer gas (dry N_2) was 0.8 L·min^{-1}. HPLC analysis was performed on a Shimadzu LC-20AD liquid chromatography with an SPD-M20A diode-matrix detector (Shimadzu, Japan) using a Phenomenex column (250×4.6 mm) and Luna C18 sorbent (5 μm). The mobile phase was H_2O:CH_3CN (95:5) at the flow rate of 1 mL/min. The analytical wavelength was 215 nm. Sorbfil SiO_2 (Russia) was used for TLC monitoring. For column chromatography SiO_2 (70–230) "Lancaster" (England) was used.

Undecylenic acid chloride (2). Thionyl chloride (4.84 g, 40.7 mmol) was added to undecylenic acid (**1**) (5.0 g, 27.1 mmol) at room temperature under an inert atmosphere of argon (Ar). The mixture was held for 6 hours (TLC control), then excess of thionyl chloride was removed under reduced pressure. Undecylenic acid chloride (**2**) was obtained in quantitative yield. IR (KBr) ν_{max} cm^{-1}: 1801 (COCl), 1640 (C=C), 3076 (=CH_2).

Oxybis(ethane-2,1-diyl)bisundec-10'-enoate (3). Diethylene glycol (1.43 g, 13.5 mmol) in dry diethyl ether (3 ml) was added to the solution of fresh acid chloride (**2**) (5.50 g, 27.1 mmol), DMAP (0.018 g, 0.15 mmol) in dry pyridine (4.40 ml, 54.2 mmol) with cooling to 5 °C in an inert atmosphere of argon. The reaction mixture was stirred for 8 hours at room temperature (TLC control), then diluted with diethyl ether (50 ml) and sequentially washed with 5 % HCl (3×5 ml), brine (3×5 ml), dried with $MgSO_4$ and evaporated. The residue was chromatographed (SiO_2, petroleum ether – Et_2O, 10:1). Yield 3.84 g (64 %), R_f=0.75 (MTBE). *m/z* $C_{26}H_{46}O_5$ (438.64) (ESI, $I_{relative.}$, %): (Scan+): 439 (48.36) $[M+H]^+$. IR (KBr) ν_{max} cm^{-1}: 3076 (CH_2=), 1738 (OC=O), 1640 (C=C). ^1H NMR ($CDCl_3$) δ ppm: 1.15-1.26 (16H, m, H-4' ÷ H-7'), 1.26–1.34 (4H, m, H-8'), 1.48–1.60 (4H, m, H-3'), 1.95 (4H, td, *J*=5.9 Hz, *J*=7.5 Hz, H-9'), 2.25 (4H, t, *J*=7.5 Hz, H-2'), 3.61 (4H, t, *J*=4.4 Hz, H-2), 4.15 (4H, t, *J*=4.4 Hz, H-1), 4.80–4.95 (4H, m, H-11'), 5.64–5.78 (2H, m, H-10'). ^{13}C NMR ($CDCl_3$) δ ppm: 24.76 (t, C-3'), 28.76, 28.94,

28.97, 29.09, 29.17 (t, C-4'÷ C-8'), 33.66 (t, C-9'), 34.03 (t, C-2'), 63.09 (t, C-1), 69.37 (t, C-2), 114.06 (t, C-11'), 138.91 (d, C-10'), 173.58 (s, C-1').

*Oxybis(ethane-2,1-diyl)bis(10'-oxoundecanoate) (**4**).* Oxygen was bubbled through a mixture of THF (70 ml), water (9 ml), $PdCl_2$ (0.33 g, 1.9 mmol), CuCl (1.04 g, 10.6 mmol) and dialkene (**3**) (2 g, 4.5 mmol) at 60 °C for 20 hours (TLC control), then the reaction mixture was diluted with ether (100 ml) and sequentially washed with 5 % HCl (3×5 ml), brine (3×5 ml), dried over $MgSO_4$ and evaporated. The residue was chromatographed (SiO_2, petroleum ether–Et_2O, 10:1). Yield 1.63 g (76 %), R_f=0.65 (MTBE). *m/z* $C_{26}H_{46}O_7$ (470.63) (ESI, $I_{relative}$, %): (Scan+): 471 (100.00) $[M+H]^+$. IR (KBr) ν_{max} cm^{-1}: 1736 (OC=O), 1716 (C=O). ^1H NMR ($CDCl_3$) δ ppm: 1.10-1.30 (16H, m, H-4' ÷ H-7'), 1.45-1.60 (8H, m, H-3', H-8'), 2.08 (6H, s, H-11'), 2.27 (4H, t, *J*=7.2 Hz, H-9'), 2.36 (4H, t, *J*=7.2 Hz, H-2'), 3.64 (4H, t, *J*=4.2 Hz, H-2), 4.17 (4H, t, *J*=4.2 Hz, H-1). ^{13}C NMR ($CDCl_3$) δ ppm: 23.68 (t, C-8'), 24.75 (t, C-3'), 28.94, 28.95, 28.98, 29.10, (t, C-4'÷ C-7'), 29.76 (q, C-11'), 34.04 (t, C-2'), 43.64 (t, C-9'), 63.15 (t, C-1), 69.01 (t, C-2), 173.66 (s, C-1'), 209.29 (s, C-10').

*Synthesis of macrocyclic compounds (**5**) and (**6**) (General method).* Adipic (or malonic) acid dihydrazide (1.06 mmol) under intensive stirring to diketone (**4**) (0.50 g, 1.06 mmol) in dioxane (9.0 ml, 106 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature (TLC control), then dioxane was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 ml), washed with water (3×5 ml), dried with $MgSO_4$, and the solvent was evaporated. To the resultant residue sequentially abs. CH_2Cl_2 (1 ml) and hexane (5 ml) were added under stirring and left to stand until the layers separated, the upper one being decanted. The remainder was rinsed with hexane (2 ml) and sublimed *in vacuo*.

*17,25-Dimethyl-1,4,7-trioxa-18,19,23,24-tetraazacyclotetratriaconta-17,24-diene-8,20,22,34-tetrone (**5**).* Yield 0.51 g (86 %). *m/z* $C_{29}H_{50}N_4O_7$ (566) (ESI, $I_{relative}$, %): (Scan+): 567 (100.00) $[M+H]^+$; (Scan–): 565 (44.64) $[M–H]^–$, 601 (100.00) $[M–H+2H_2O]^–$. IR (KBr) ν_{max} cm^{-1}: 3198 (NH), 1734 (COO), 1683 (CONH), 1653 (C=N). ^1H NMR ($CDCl_3$) δ ppm: 1.18 (6H, s, CH_3-17, CH_3-25), 1.32–1.46 (8H, m, H-12, H-13, H-29, H-30), 1.46–1.58 (8H, m, H-11, H-14, H-28, H-31), 1.73–1.86 (8H, m, H-10, H-15, H-27, H-32), 2.07–2.20 (4H, m, H-16, H-26), 2.22 (4H, t, *J*=6.5 Hz, H-9, H-33), 2.23 (2H, s, H-21), 3.60 (4H, t, *J*=4.5 Hz, H-3,H-5), 4.12 (4H, t, *J*=4.5 Hz, H-2, H-6), 9.41 (2H, br.s, H-19, H-23). ^{13}C NMR ($CDCl_3$) δ ppm: 15.76 (s, CH_3-17, CH_3-25), 24.50 (t, C-15, C-27), 24.72 (t, C-10, C-32), 28.67, 28.93, 29.06, 29.16, (t, C-11÷C-14, C-28÷C-31), 34.00 (t, C-9, C-33), 38.99 (t, C-16, C-26), 53.51 (t, C-21), 63.11 (t, C-2, C-6), 68.98 (t, C-3, C-5), 158.80 (s, C-17, C-25), 173.61 (s, C-20, C-22), 177.55 (s, C-8, C-34).

*17,27-Dimethyl-1,4,7-trioxa-18,19,25,26-tetraazacyclohexatriaconta-17,26-diene-8,20,24,36-tetrone (**6**).* Yield 0.61 g (98 %). *m/z* $C_{31}H_{54}N_4O_7$ (594.3) (ESI, $I_{relative}$, %): (Scan+): 595 (100.00) $[M+H]^+$; (Scan–): 593 (48.26) $[M–H]^–$, 629 (100.00) $[M–H+2H_2O]^–$. IR (KBr) ν_{max} cm^{-1}: 3198 (NH), 1737 (COO), 1699 (CONH), 1668 (C=N). ^1H NMR ($CDCl_3$) δ ppm: 1.18–1.38 (16H, m, H-11÷H-14, H-30÷H-33), 1.50-1.60 (4H, m, H-10, H-34), 1.73–1.80 (4H, m, H-15, H-29), 1.90–2.00 (2H, m, H-22), 2.00 (6H, s, CH_3-17, CH_3-27), 2.15 (4H, t, *J*=6.9 Hz, H-21, H-23), 2.25 (4H, t, *J*=7.3 Hz, H-16, H-28), 2.66 (4H, t, *J*=6.3 Hz, H-9, H-35), 3.66 (4H, t, *J*=5.0 Hz, H-3, H-5), 4.18 (4H, t, *J*=5.0 Hz, H-2,H-6), 9.20 (2H, br.s, H-19, H-25). ^{13}C NMR ($CDCl_3$) δ ppm: 15.53 (s, CH_3-17, CH_3-27), 19.40 (t, C-22), 23.38 (t, C-15, C-29), 24.74 (t, C-10, C-34), 28.96, 29.04, 29.08, 29.13, (t, C-11÷C-14, C-30÷C-33), 32.06 (t, C-9, C-35), 34.02 (t, C-16, C-28), 38.79 (t, C-21, C-23), 63.13 (t, C-2, C-6), 68.98 (t, C-3, C-5), 152.91 (s, C-17, C-27), 173.61 (s, C-8, C-36), 175.97 (s, C-20, C-24).

*5,31-Dimethyl-15,18,21-trioxa-3,4,32,33-tetraaza-1(2',6')-pyridinocyclotetratriaconta-4,31-diene-2,14,22,34-tetrone (**7**).* 2,6-Pyridinedicarboxylic acid hydrazide (0.19 g, 1.06 mmol) in H_2O (0.19 ml, 10.6 mmol) under intensive stirring to diketone (**4**) (0.5 g, 1.06 mmol) in dioxane (9.0 ml, 106 mmol) was added. The reaction mixture was stirred for 24 hours at room temperature (TLC control), then dioxane was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 ml), washed with water (3×5 ml), dried over $MgSO_4$, and the solvent was evaporated. To the resultant residue sequentially abs. CH_2Cl_2 (1 ml) and hexane (5 ml) were added under stirring and left to stand until the layers separated, the upper one being decanted. The remainder was rinsed with hexane (2 ml) and sublimed *in vacuo*. Yield 0.55 g (82 %). *m/z* $C_{33}H_{51}N_5O_7$ (629.78) (ESI, $I_{relative}$, %): (Scan+): 630 (59.83) $[M+H]^+$, 648 (28.36) $[M+H_2O]^+$. IR (KBr) ν_{max} cm^{-1}: 3336 (NH), 1737 (COO), 1714 (CONH), 1630 (C=N). ^1H NMR ($CDCl_3$) δ ppm: 1.08–1.40 (4H, m, H-8, H-28), 1.20–1.40 (12H, m, H-9÷H-11, H-25÷H-27), 1.50–1.70 (8H, m, H-7, H-12, H-24, H-29), 2.00 (6H, s, CH_3-5, CH_3-31), 2.33 (4H, t, *J*=6.9 Hz, H-13, H-23), 2.41 (4H, t, *J*=7.2 Hz, H-6, H-30), 3.61 (4H, br.s., H-17, H-19), 4.13 (4H, br.s., H-16, H-20), 7.99 (1H, br.s, H-4'), 8.31 (2H, br.s, H-3', H-5'), 10.30 (2H, br.s., H-3, H-33). ^{13}C NMR ($CDCl_3$) δ ppm: 15.53 (q, CH_3-5, CH_3-31), 23.66 (t, C-12, C-24), 24.72 (t, C-7, C-29), 26.54 (t, C-10, C-26), 29.07 (t, C-11, C-25), 29.75 (t, C-9, C-27), 34.02 (t, C-8, C-28), 39.12 (t, C-13, C-23), 43.61 (t, C-6, C-30), 63.13 (t, C-16, C-20), 68.97 (t, C-17, C-19), 125.89 (d, C-4'), 139.19 (d, C-3', C-5'), 148.47 (s, C-2', C-6'), 158.91 (s, C-2, C-34), 159.14 (s, C-5, C-31), 176.63 (s, C-14, C-22). IR (KBr) ν_{max} cm^{-1}: 3336 (NH), 1737 (COO), 1714 (CONH), 1630 (C=N).

Result and Discussion

The structures of the resulting macrocycles (**5-7**) were confirmed by IR, ^1H and ^{13}C NMR spectroscopy and GC/MS. The chemical purity (~95 %) was established by HPLC.

IR spectra of (**5-7**) showed lacked absorption bands (1716 cm^{-1}) which are characteristic of the ketone groups of key intermediate (**4**). Bands in the IR spectra of (**5-7**) were observed at 1630–1668 cm^{-1} (C=N), 1664–1699 cm^{-1} (CONH), and 3198–3336 cm^{-1} (NH). These proved that macrocycles with hydrazide groups have been formed.

Structures of the macrocycles (**5-7**) were studied using ^{13}C NMR and ^1H NMR spectroscopy. The NMR spectra of (**5-7**) were analyzed by comparison with those of the starting compound (**4**) and hydrazides of dicarboxylic acids.

In the ^{13}C NMR spectra of products (**5-7**) there are no signals of carbonyl C atoms of the starting compound (**4**) (209.29 ppm). Furthermore, ^1H NMR spectra of the macrocycles (**5-7**) lacked resonances of the hydrazine group (NH_2NH) (4.64–4.80 ppm). These facts indicated that the products were not linear substitution products.

^{13}C NMR spectra of (**5-7**) contained resonances for ester C atoms (177.55 ppm (**5**), 173.61 ppm (**6**) and 176.63 ppm (**7**)) and resonances of NH–C=O groups of the starting dihydrazides (~162 ppm) that were shifted (173.61 ppm (**5**), 175.97 ppm (**6**) and 158.91 ppm (**7**)). There were also singlets for C=N (158.80 ppm (**5**), 152.91 ppm (**6**) and 159.14 ppm (**7**)) and two quartets for *cis*-CH_3 (15.76 ppm (**5**), 15.53 ppm (**6**) and (**7**)), the chemical shifts of which corresponded to C atoms of two magnetically equivalent CH_3–C=N groups. The appearance of triplets (38.99 ppm (**5**) and 34.02 ppm (**6**), 43.61 ppm (**7**)) for two CH_2C=N groups also confirmed that the hydrazides (CH_2C=N–NH–C=O) have been formed. ^1H NMR spectra of (**11**) and (**12**) showed weak-field resonances (9.41 ppm (**5**), 9.20 ppm (**6**) and 10.30 ppm (**7**)), the chemical shifts and integrated intensities of which corresponded to two protons of NHC=O groups in the macrocycles.

All these spectral data indicated that macrocycles (**5-7**) were formed. This was also confirmed by mass spectra.

Mass spectra of the synthesized compounds (**3-7**) were studied using electrospray ionization (APCI) with simultaneous recording of positive and negative ions at capillary potentials. Very intensive peaks for protonated MH^+ and deprotonated $[M–H]^–$ ions in addition to their ionic associates with molecules (H_2O) were recorded in the mass-spectrometric study of (**3-7**). This could be considered as a proof of the existence of compounds with the corresponding molecular weights.

Conclusions

The synthesis of three potentially biologically and pharmacologically active 34- and 36-membered macrolides containing oxa-, ester- and dihydrazide fragments was developed starting from commercially available undecylenic acid. The evidence is given for the structure of the obtained macrocycles using IR and NMR spectroscopy, and mass spectrometry.

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