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

Marina P. Yakovleva, Galina R. Mingaleeva, Kseniya S. Denisova, Timur R. Nugumanov, Aleksandr G. Tolstikov, and Gumer Yu. Ishmuratov

Ufa Institute of Chemistry of the Russian Academy of Sciences, 450054 Ufa, Russia

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 diethyleneglycol gave functionalized α,ω-dialkene (3). This α,ω-dialkene (3) was oxidized by Wakker-Tsui 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

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.
of 10 eq. of water because of poor solubility of the hydra-
zide 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$_2$O with TMS internal standard on a Bruker AM-500 spectrometer (operating frequency 500.13 MHz for $^1$H; 126.76 MHz for $^{13}$C). Mass spectra were recorded on a LC/MS 2010 EV Shimadzu instrument (syringe input, sample solution in CH$_3$CN 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$_2$O:CH$_3$CN (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) $\nu_{\text{max}}$ cm$^{-1}$: 1801 (СОCl), 1640 (С=С), 3076 (=СН$_2$).

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$_2$O, 10:1). Yield 3.84 g (64 %), $R_f$ =0.75 (MTBE), m/z C$_{26}$H$_{46}$O$_5$ (438.64) (ESI, I$_{\text{relative}}$, %): (Scan+): 439 (48.36) [M+H$^+$]. IR (KBr) $\nu_{\text{max}}$ cm$^{-1}$: 3076 (CH$_2$=), 1738 (OС=О), 1640 (C=C).

1$^H$ NMR (CDCl$_3$) $\delta$ ppm: 1.15-1.26 (16Н, m, H-4' ÷ H-7'), 1.26–1.34 (4Н, m, H-8'), 1.48–1.60 (4Н, m, H-3'), 1.95 (4Н, td, $J$=5.9 Hz, J=7.5 Hz, H-9'), 2.25 (4H, t, $J$=7.5 Hz, H-2'), 3.61 (4Н, 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'). 1$^3$С NMR (CDCl$_3$) $\delta$ ppm: 115-1.26 (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').
Oxidicthene-2,1-diylisobis(10-oxosudeneaconate) (4). Oxygen was bubbled through a mixture of THF (70 ml), water (9 ml), PdCl₂ (0.33 g, 1.9 mmol), CuCl (1.94 g, 10.6 mmol) and diazene (3 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 MgSO₄ and evaporated. The residue was chromatographed (SiO₂ (0.33 g, 1.9 mmol), CuCl₂ (1.04 g, 10.6 mmol) and dialkene (>90 %), 1.32–1.46 (8H, m, H-12, H-13, H-29, H-30), 2.27 (4H, t, J=7.2 Hz, H-2), 2.36 (4H, t, J=4.2 Hz, H-2), 4.17 (4H, t, J=4.2 Hz, H-1). ¹C NMR (CDCl₃) δ ppm: 23.68 (t, C-8'), 24.75 (t, C-3'), 28.94, 28.95, 29.07, 29.16 (t, C-9', C-10'), 29.17 (t, C-12, C-24), 32.97 (q, C-11', C-13'), 34.04 (t, C-16', C-22), 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) (0.5 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 CH₂Cl₂ (50 ml), washed with water (3×5 ml), dried with MgSO₄ and the solvent was evaporated. To the resultant residue sequentially abs. CH₂Cl₂ (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 submitted in vacuo. Yield 0.51 g (86 %), m/z C₂₆H₄₆N₄O₂ (470.63) (ESI, m+), % (Scan+): 471 (100.00) [M+H]+. IR (KBr) v max cm⁻¹: 3198 (NH), 1737 (COO), 1699 (CONH), 1594 (C=N). Furthermore, ¹H NMR spectra of (4) showed no signals of carbonyl C atoms of the starting compound (4) (209.29 ppm). In the ¹C NMR spectra of (4) there were observed at 1630–1668 cm⁻¹ (C=O), 1664–1699 cm⁻¹ (CONH), and 3198–3336 cm⁻¹ (NH). These proved that macrocycles with hydrazide groups have been formed.

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 CH₂Cl₂ (50 ml), washed with water (3×5 ml), dried over MgSO₄ and the solvent was evaporated. To the resultant residue sequentially abs. CH₂Cl₂ (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 submitted in vacuo. Yield 0.55 g (82 %), m/z C₃₁H₅₄N₄O₂ (629.78) (ESI, m+), % (Scan+): 630 (59.38 %) [M+H]¹, 648 (28.36) [M+H]², IR (KBr) v max cm⁻¹: 3336 (NH), 1737 (COO), 1714 (CONH), 1630 (C=N), H NMR (CDCl₃) 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, CH₂, H-5, H-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). ¹C NMR (CDCl₃) δ ppm: 15.53 (q, CH₂-5, CH₃-31), 23.66 (t, C-12, C-24), 24.72 (t, C-7, C-29), 25.64 (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) v 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 ¹C 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=O), 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 ¹C 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 dicarbonyl acids.

In the ¹C 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 (NH₂) (4.64–4.80 ppm). These facts indicated that the products were not linear substitution products.

¹C NMR spectra of (5-7) contained resonances for easter 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 (158.50 ppm (5), 152.91 ppm (6) and 159.14 ppm (7)) and two quartets for C=N–NH–C=O groups of the starting compounds (4). The chemical shifts of which corresponded to C atoms of two magnetically equivalent CH₃–C=N groups also confirmed that the macrocycles with hydrazide groups have been formed.

Triplet of protons of NHC=O groups in the macrocycles.

The appearance of triplets (38.99 ppm (5) and 34.02 ppm (6), 43.61 ppm (7) for two CH₂C₅N groups also confirmed that the hydrazides (CH₂C₅N=NH–C=O) have been formed. 'H 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.
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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 (H2O) 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.

References

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Received 18.07.2017
Accepted 30.07.2017