

Synthesis of Macrolides with Hydrazone Fragments from Tetrahydropyran and 2,6-Pyridinedicarboxylic Acid

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Dedicated to the Corresponding Member of Russian Academy of Sciences Oscar I. Koifman on the occasion of his 70th Anniversary

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The synthesis of two potentially useful 23- and 29-membered macrolides containing a pyridine ring and dihydrazone fragments was developed starting from tetrahydropyran. It was based on [1+1]-condensation of 7'-oxooctyl-7-oxooctanoate and bis(7-oxooctyl)hexanedioate with 2,6-pyridinedicarboxylic acid hydrazone. The structure of the macrocycles obtained was confirmed using IR and NMR spectroscopy and mass spectrometry.

Keywords: Tetrahydropyran, macrolides with dihydrazone fragments, [1+1]-condensation, synthesis.

Синтез макролидов с гидразидными фрагментами из производных тетрагидропирана и 2,6-пиридиндикарбоновой кислоты

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Посвящается член-корреспонденту РАН Оскару Иосифовичу Койфману по случаю его 70-летнего юбилея

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Исходя из тетрагидропирана разработан синтез двух потенциально полезных 23- и 29-членных макролидов, содержащих пиридиновое кольцо, сложноэфирные группы и гидразидные фрагменты, на основе [1+1]-конденсации 7'-оксооктил-7-оксооктаноата и бис(7-оксооктил)гександиоата с гидразидом 2,6-пиридиндикарбоновой кислоты. Структура полученных соединений была подтверждена с помощью ИК и ЯМР спектроскопии и масс-спектрометрии.

Ключевые слова: Тетрагидропиран, макролиды с гидразидными фрагментами, [1+1]-конденсация, синтез.

We previously proposed the synthesis from tetrahydropyran (**1**) of α,ω -diketones **2** and **3** containing one (**2**) or two (**3**) ester groups.^[1,2] Their [1+1]-condensation with hydrazine hydrate or dihydrazides of malonic, glutaric, adipic,^[1,2] azelaic, sebacic, 7-oxabicyclo[2.2.1]heptenoic^[3] and tartaric^[4,5] acids led to macroheterocycles containing one or two ester groups and azine or dihydrazone fragments. One of the synthesized macrolides **4** showed a significant (at the level of erythromycin) antibacterial activity *in vitro* and *in vivo* against the museum and field strains of pathogenic microorganisms (*Staphylococcus aureus*, *Escherichia coli* and *Pseudomonas aeruginosa*).^[6]

In continuation of these studies we performed [1+1]-condensation of α,ω -diketone (**2**) or (**3**) with 2,6-pyridinedicarboxylic acid hydrazone (**5**) that was prepared using the standard method.^[7]

Introduction of 2,6-pyridinedicarboxylic acid to the macrocyclic fragment is due to the fact that its derivatives exhibit a wide range of pharmacological activity (such as, antibacterial, anti-inflammatory, anticoagulant and anti-tumor),^[8] and derivatives of 2,6-pyridinedicarboxylic acid are widely used in chemistry of a complex formation.^[9]

Experimental

Analyzes were performed on the equipment at the Center for the Collective Use «Chemistry» of the Institute of Organic Chemistry of Ufa Scientific Centre 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 CDCl₃ and D₂O with TMS internal standard on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for ¹H; 75.47 MHz for ¹³C). TLC monitoring used Sorbfil SiO₂ (Russia).

Mass spectra were recorded on a LC/MS 2010 EV Shimadzu instrument (syringe input, sample solution in CH₃CN at flow rate 60 μ L/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 N₂) was 0.8 L·min⁻¹. HPLC analysis was performed on a Shimadzu LC-20AD liquid chromatograph with an SPD-M20A diode-matrix detector (Shimadzu, Japan) using a Phenomenex column (250×4.6 mm) and Luna C18 sorbent (5 μ m). The mobile phase was H₂O:CH₃CN (95:5) at the flow rate of 1 mL/min. The analytical wavelength was 215 nm.

2,6-Pyridinedicarboxylic acid hydrazone, 5. ¹H NMR (D₂O) δ ppm: 4.62 (4H, s, NH₂), 8.15 (3H, s, Ar-H), 10.60 (2H, s, NH). ¹³C NMR (D₂O) δ ppm: 123.82 (d, C-3, C-5), 139.46 (d, C-4), 148.41 (s, C-2, C-6), 162.02 (s, C(O)NH). IR (KBr) ν_{\max} cm⁻¹: 3270 (NHNH₂), 1689 (C(O)NH).

Synthesis of macrocyclic compounds 6 and 7 (general procedure). The 2,6-pyridinedicarboxylic acid hydrazone (**5**, as described in ^[6]) (0.244 g, 1.0 mmol) in 1.8 mL of H₂O, was slowly added under vigorous stirring to 1.0 mmol of α,ω -diketones **2** or **3** in 8.5 mL of dioxane. The mixture was stirred for 48 h (monitoring TLC) and dioxane was evaporated under reduced pressure. The residue was dissolved in 20 mL of CH₂Cl₂, and washed with water (3×5 mL), dried with MgSO₄, and evaporated. The residue was stirred with 10 ml of hexane, and the solution was separated by decanting. The precipitate represented a macroheterocycle **6** or **7**.

5,19-Dimethyl-12-oxa-3,4,20,21-tetraaza-1(2,6)-pyridinacyclodocosaphane-4,19-diene-2,11,22-trione, 6. Yield 0.104 g

(37%). *m/z* C₂₃H₃₃N₅O₄ (443.25) (ESI, *I*_{relative}, %): (Scan+): 444.2 (2.2) [M+H]⁺, 466.4 (39.1) [M+Na]⁺, 484.35 (26.8) [M+Na+H₂O]⁺; (Scan-): 442.3 (73.7) [M-H]⁻, 460.35 (41.7) [M-H+H₂O]. ¹H NMR (CDCl₃) δ ppm: 1.20-1.41 (2H, m, H-26), 1.47-1.70 (10H, m, H-4, H-5, H-6, H-23, H-24), 2.08 (6H, s, CH₃-8, CH₃-21), 2.28 (2H, t, *J* 7.4, H-3), 2.42 (4H, t, *J* 8.0, H-7, H-22), 8.09 (1H, t, *J* 7.7, H-14), 8.45 (2H, t, *J* 7.7, H-13, H-15), 10.25 (2H, s, NH). ¹³C NMR (CDCl₃) δ ppm: 15.41 (q, CH₃-8, CH₃-21), 25.72 (t, C-5), 28.43 (t, C-6, C-23), 28.56 (t, C-25), 28.65 (t, C-4), 28.74 (t, C-24), 34.07 (t, C-26), 39.08 (t, C-3), 43.42 (t, C-22), 43.57 (t, C-7), 64.26 (t, C-27), 126.16 (d, C-13, C-15), 139.45 (d, C-14), 148.56 (s, C-12, C-16), 158.97 (s, C-8, C-21), 161.04 (s, C-11, C-18), 173.75 (s, C-2). IR (KBr) ν_{\max} cm⁻¹: 3337 (NH), 1731 (CH₂COO), 1699 (CONH), 1635 (C=N).

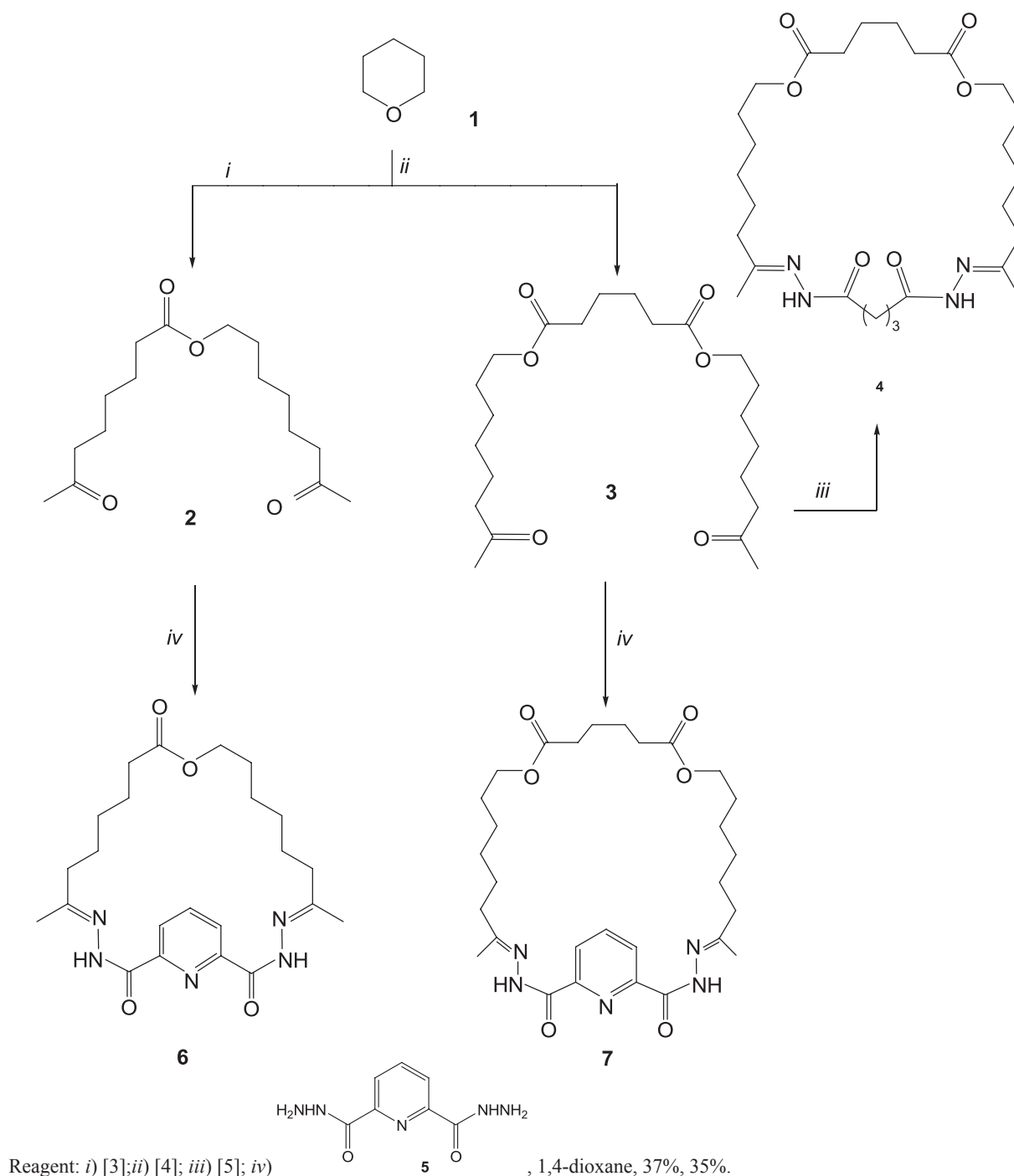
5,26-Dimethyl-12,19-dioxa-3,4,27,28-tetraaza-1(2,6)-pyridinacyclotriokonta-4,19-diene-2,13,18,29-tetraone, 7.

Yield 0.139 g (35%). *m/z* C₂₉H₄₃N₅O₆ (557.32) (ESI, *I*_{relative}, %): (Scan+): 558.4 (2.3) [M+H]⁺, 280.35 (100) [M+Na]⁺, 598.3 (16.2) [M+Na+H₂O]⁺; (Scan-): 556.35 (100) [M-H]⁻, 574.35 (20.4) [M-H+H₂O]⁻, 592.35 (2.0) [M-H+2H₂O]⁻. ¹H NMR (CDCl₃) δ ppm: 1.31-1.42 (8H, m, H-11, H-12, H-31, H-32), 1.60-1.68 (8H, m, H-4, H-5, H-13, H-30), 2.18 (6H, s, CH₃-15, CH₃-28), 2.28-2.32 (4H, m, H-10, H-33), 2.42 (4H, t, *J* 6.8, H-14, H-29), 2.51 (4H, t, *J* 6.8, H-3, H-6), 4.07 (4H, t, *J* 6.7, H-9, H-34), 8.11 (1H, t, *J* 7.6, H-21), 8.47 (2H, d, *J* 7.6, H-20, H-22), 10.20 (2H, s, NH). ¹³C NMR (CDCl₃) δ ppm: 15.27 (q, CH₃-15, CH₃-28), 23.59 (t, C-11, C-32), 24.30 (t, C-4, C-5), 25.71 (t, C-13, C-30), 28.41 (t, C-12, C-31), 33.90 (t, C-10, C-33), 39.12 (t, C-3, C-6), 43.56 (t, C-14, C-29), 64.29 (t, C-9, C-34), 126.26 (d, C-20, C-22), 139.46 (d, C-21), 148.55 (s, C-19, C-23), 158.83 (s, C-15, C-28), 160.85 (s, C-18, C-25), 173.44 (s, C-2, C-7). IR (KBr) ν_{\max} cm⁻¹: 3343 (NH), 1735 (CH₂COO), 1683 (CONH), 1634 (C=N).

Results and Discussion

[1+1]-Condensation of α,ω -diketones **2** or **3** with a 2,6-pyridinedicarboxylic acid dihydrazone (**5**) in dioxane-water system under high dilution at room temperature resulted in potentially biologically active 23- (**6**) and 29- (**7**)-membered macroheterocycles containing a pyridine ring and dihydrazone fragments and one or two ester groups with ~40% conversion of the initial **2** or **3**.

The structures of the synthesized macroheterocycles **6** and **7** were confirmed by IR, ¹H NMR, and ¹³C NMR spectroscopy and GC/MS. The chemical purity (~95%) was established by HPLC. The IR spectrum of compounds **6** and **7** do not have any absorption bands in the region of 1718 cm⁻¹ (**6**) and 1703 cm⁻¹ (**7**), which are characteristic for the ketone groups of key intermediates **2** and **3**. The IR spectra of **6** and **7** contain bands at 1630 cm⁻¹ (C=N), 1664-1671 cm⁻¹ (CONH), and 3354-3455 cm⁻¹ (NH). This proves that macrocycles with hydrazone groups have been formed. Structures of the macrocycles **6** and **7** were studied using ¹³C NMR and ¹H NMR spectrometry. The NMR spectra of **6** and **7** were analyzed by comparison with those of the starting compounds **2** and **3** and hydrazone of dicarboxylic acids **5**. The ¹³C NMR spectra of the reaction products **6** and **7** did not show any signals of carbonyl carbon atoms of initial compounds **2** and **3** (208.86 ppm and 208.99 ppm in **6** and 208.66 ppm in **7**). Furthermore, ¹H NMR spectra of the macrocycles **6** and **7** did not show resonances of the hydrazone group (NH₂NH) (~4.63 ppm). These facts indicated that the products were not the linear substitution products. ¹³C NMR spectra of **6** and **7** contained resonances for ester C atoms



(173.75 (6) and 173.44 ppm (7)) and resonances of NH–C=O groups of the starting dihydrazides (162.02 ppm) that were shifted (161.04 ppm (6) and 160.85 ppm (7)). There were also singlets for C=N (158.97 ppm (6) and 158.83 ppm (7)) and two quartets for *cis*-CH₃ (15.41 ppm (6) and 15.27 ppm (7)), the chemical shifts of which corresponded to C atoms of two magnetically equivalent CH₃-C=N groups. The appearance of triplets (43.42 and 43.57 ppm (6), 43.56 ppm (7)) for two CH₂C=N groups also confirmed that the formation of hydrazides (CH₂C=N–NH–C=O). ¹H NMR spectra of 6 and 7 showed downfield resonances (10.25 ppm (6) and 10.20 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 indicate that macrocycles 6 and 7 were formed. This was also confirmed by mass

spectra. Mass spectra of the synthesized compounds 6 and 7 were studied using electrospray ionization (ESI) with simultaneous recording of positive and negative ions at capillary potentials of 4.5 and 3.5 kV, respectively. Very intensive peaks for protonated MH⁺ and deprotonated [M–H][–] ions in addition to their ionic associates with ions (Na⁺, K⁺) and molecules (H₂O) were recorded in the mass-spectrometric study of 6 and 7. This may be considered to be a proof of existence of the compounds with appropriate molecular weights.

Conclusions

The synthesis of two potentially biologically and pharmacologically active 23- and 29-membered macrolides

containing pyridine ring and dihydrazone fragments was developed starting from tetrahydropyran as available petrochemical product. It was based on [1+1]-condensation of 7-oxooctyl-7-oxooctanoate and bis(7-oxooctyl)hexanedioate with 2,6-pyridinedicarboxylic acid hydrazone. The evidence is given for the structure of the obtained macrocycles using IR and NMR spectroscopy and mass spectrometry.

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