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Synthesis of Macrolides with Fragments of Diethylene Glycol and Hydrazides of Dicarboxylic Acids from 7-Oxooctanoic Acid

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Based on the available 7-oxooctanoic acid, syntheses of two potentially useful macrolides with diethylene glycol and dihydrazide fragments have been developed using at the key stages [2+1]-interaction of 7-oxooctanoic acid with diethylene glycol ditosylate and [1+1]-condensation of the resulting α,ω-diketodiester with dihydrazides of adipic and L-(+)-tartaric acids. The structure of the obtained compounds was established using IR and NMR spectroscopy and confirmed by chromatography-mass spectrometry.

Keywords: 7-Oxooctanoic acid, diethylene glycol, macrolides with ethylene glycol and dihydrazide fragments, [2+1]- and [1+1]-condensations.

Синтез макролидов с фрагментами диэтиленгликоля и гидразидов дикарбоновых кислот из 7-оксооктановой кислоты

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Исходя из доступной 7-оксооктановой кислоты разработаны синтезы двух потенциально полезных макролидов с диэтиленгликольным и дигидразидными фрагментами с использованием на ключевых стадиях [2+1]-взаимодействия последней с дитозилатом диэтиленгликоля и [1+1]-конденсации образующегося α,ω-дикетодиэфира с дигидразидами адипиновой и L-(+)-винной кислот. Структура полученных соединений установлена с помощью ИК- и ЯМР-спектроскопии и подтверждена данными хромато-масс-спектрометрии.

Ключевые слова: 7-Оксооктановая кислота, диэтиленгликоль, макролиды с этиленгликольными и дигидразидными фрагментами, [2+1]- и [1+1]-конденсации.

Introduction

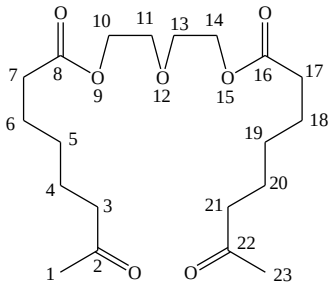
Earlier, we have studied[1,2] the by-products of the Debner reaction of 7-oxooctanal with malonic acid in the synthesis of 9-oxo-2*E*-decenoic acid, a multifunctional pheromone of the honey bee *Apis mellifera* L. – 7-oxooctanoic acid (**1**) was detected. This ketoacid **1** was also obtained from 2-acetylcyclohexanone by boiling in aqueous NaOH (yield 50 %),[3] when interacting with $Fe(OTf)_3$ at

80°C (87%)[4] or indium-catalyzed retro-Kleisen condensation.[5] It was also formed by the photochemical reaction of acetone with 4-pentenic acid (77 %)[6] and by the allylic oxidation of 1-methylcycloheptene (75 %).[7]

7-Oxooctanoic acid (**1**) is widely used in directed organic synthesis, *e.g.* for obtaining 9-oxo-2*E*-decenoic acid,[8,9] for synthesis of (±)-frontalin[10] – an aggregation pheromone of the bark beetle *Dendroctonus pseudotsugae*, a pest of Douglas fir. Based on it, a stereospecific syntheses of 23-hydroxyundecylprodiginins as antimalarial agents[11] and analogues of ceramide[12] – drugs for the treatment of neuron diseases and brain protection, are presented As a substituent in the side chain, ketoacid **1** was used in the synthesis of a highly effective antistof for the detection of cyclic triacetone triperoxide,[13] and in the synthesis of 2β-piperazine-substituted steroid derivatives as anticancer agents.[14] On its basis, a new series of heteroarylmethoxyphenylalkoxyiminoalkyl carboxylic acids were also obtained as inhibitors of leukotriene biosynthesis[15] and catecholamine conjugates[16] as potential β-adrenergic agonists. The article[17] describes the synthesis of esters of 1,7-octanediol obtained from 7-oxooctanoic acid (1) as the basis of compositions of lipid nanoparticles for intracellular delivery of therapeutic agents. There is also data on the formation of small cycles based on its oxo-group. Thus, ketoacid **1** was used to form a 1,8-naphthyridine cycle in the synthesis of nitrogen-containing compounds – therapeutic and radiodiagnostic agents in disorders associated with integrin,[18] to create a pyrimidine cycle in the synthesis of water-soluble fluorescent markers of the near infrared range for biological labeling, [19] or to obtain an indole cycle in the synthesis of analogues of the prostaglandin D2 receptor antagonist (PGD2).[20] An eight-membered 2,2-disubstituted aminocarbonyl lactam[21] was also obtained on the basis of 7-oxooctanoic acid (**1**) by an "intramolecular" three-component Ugi reaction;[22] ((E)-4-(tributylstannyl)but-3-enyloxy)carbonyl)hept-1-en-2-yltrifluoromethylsulfonate, as well as 22-membered diallenic diolide[23] were obtained by intermolecular reaction [1+1]-condensation of phosphonium salt from 7-(2-bromoacetoyloxy)octanoic acid chloride. For the synthesis of potentially useful macroheterocycles with ester and dihydrazide fragments, ketoacid **1** was not used.

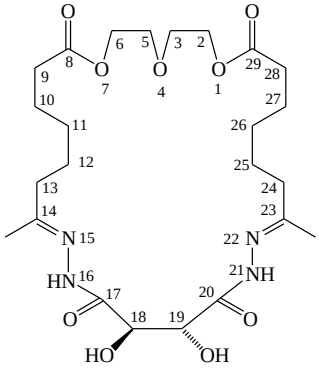
Experimental

The spectra were recorded at the Center for the Collective Use "Chemistry" of the Ufa Institute of Chemistry of the UFRC RAS and RCCU "Agidel" of the UFRC RAS. IR spectra recorded on the a IR-Prestige-21 (Fourier Transform Spectrophotometer–Shimadzu) in a thin layer. ^{1}H and ^{13}C NMR spectra were recorded on a "Bruker AM-500" (Bruker, Billerica, MA, USA, 500 and 125.5 MHz, respectively, δ, ppm, Hz) in $CDCl_3$, internal standard tetramethylsilane. Mass spectra were obtained on a liquid chromatograph–mass spectrometer LCMS-2010 EV (Shimadzu, Kyoto, Japan). Optical rotations were measured on a polarimeter "Perkin-Elmer 241 MC" (Perkin-Elmer, Waltham, MA, USA) in a tube length of 1 dm. Thin-layer chromatography analyses were performed on Sorbfil plates (Sorbpolimer, Krasnodar, Russian Federation). Substances were detected by 10% H_2SO_4 with subsequent heating to 100–120 °C for 2–3 min. The data of the elemental analysis of all compounds corresponded to the calculated ones. To carry out the reactions and isolate the obtained compounds, were used petroleum ether (PE) 40-70 °C, methyl *tert*-butyl ether (MTBE), methylene chloride, acetonitrile, purified and dried according to standard methods.[24]



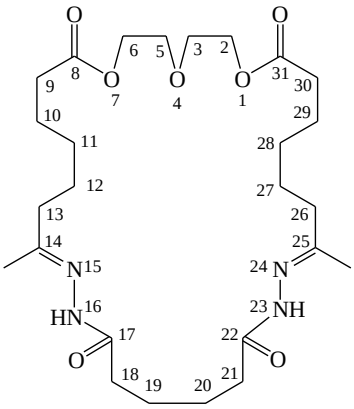
*2,8,16,22-Tetraoxo-9,12,15-trioxatricosan (**5**).* A solution of 1.25 g (7.9 mmol) ketoacid **1**, received according to [1], and 1.09 g K_2CO_3 (7.9 mmol) in 25 mL of dry acetonitrile was refluxed for 1 h in an inert atmosphere (Ar), then while stirring 1.61 g (3.9 mmol) of the triethylene glycol ditosylate, prepared according to [25], was added dropwise in 25 mL of acetonitrile. Mixture was refluxed for 120 h, acetonitrile was evaporated, the resulting precipitate was dissolved in CH_2Cl_2 (35 mL), washed with saturated solution of NaCl (3×5 mL), dried with Na_2SO_4, evaporated, the precipitate was chromatographed (SiO_2, PE-MTBE, 5:1). Yield: 1.98 g (65 %). R_f 0.5 (MTBE). *m/z* (APCI) %: 387.3 (100.0) $[M+H]^+$, 405.3 (49.0) $[M+H+H_2O]^+$. $C_{20}H_{34}O_7$. Calculated: [386.48]. IR (KBr) ν_{max} cm^{-1}: 1716 (C=O), 1734 (C(O)-O). ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.84–0.87 (4H, m, H-5, H-19), 1.49–1.60 (8H, m, H-4, H-6, H-18, H-20), 2.07 (6H, s, H-1, H-23), 2.32 (4H, t *J* = 7.4 Hz, H-7, H-17), 2.42 (4H, t *J* = 7.4 Hz, H-3, H-21), 3.53 (4H, t *J* = 6.0 Hz, H-11, H-13), 4.12 (4H, t *J* = 6.0 Hz, H-10, H-14). ^{13}C NMR δ_C ppm: 22.68 (CH_2, C-4, C-20), 24.45 (CH_2, C-6, C-18), 27.96 (CH_2, C-5, C-19), 30.02 (CH_3, C-1, C-23), 33.43 (CH_2, C-7, C-17), 44.48 (CH_2, C-3, C-21), 63.38 (CH_2, C-10, C-14), 69.49 (CH_2, C-11, C-13), 173.23 (C, C-8, C-16), 208.86 (C, C-2, C-22).

*General method for obtaining O- and N-containing macroheterocycles **2** and **3**.* To 0.96 g (2.5 mmol) of diketone **5** in 22 mL of dioxane with intensive stirring, 2.5 mmol of adipic or L-(+)-tartaric acid dihydrazide[25] was slowly added into H_2O (4.5 mL), stirred for 48 h (TLC control), dioxane was evaporated at reduced pressure. The residue was dissolved in 50 mL of CH_2Cl_2, washed with H_2O (3×5 mL), dried with Na_2SO_4 and evaporated, then washed with 10 mL of hexane and evaporated.



*(14E,18R,19R,22E)-18,19-Dihydroxy-14,23-dimethyl-1,4,7-trioxa-15,16,21,22-tetraazacyclononacose-14,22-diene-8,17,20,29-tetraone (**2**).* Yield: 0.43 g (33 %), yellowish thick oily liquid. $[\alpha]_D^{20}$ –19.0° (*c* 0.1; CH_2Cl_2). *m/z* (APCI) %: 529.4 (100.0) $[M+H]^+$, 563.5 (100.0) $[M-H+Cl]^-$. $C_{24}H_{40}N_4O_9$. Calculated: [528.60]. IR (KBr) ν_{max} cm^{-1}: 1653 (CN), 1733 (OC(O)), 3342

(NH). ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.87–0.97 (4H, m, H-11, H-26), 1.52–1.66 (8H, m, H-10, H-12, H-25, H-27), 1.82 (6H, s, CH_3-14, CH_3-23), 2.33 (4H, t J = 7.4 Hz, H-9, H-28), 2.48 (4H, t J = 7.0 Hz, H-13, H-24), 3.53 (4H, t J = 6.0 Hz, H-3, H-5), 4.13 (4H, t J = 6.0 Hz, H-2, H-6), 4.30 (2H, d J = 6.5 Hz, H-18, H-19), 5.90 (2H, s, OH), 9.61 (2H, br.s, NH). ^{13}C NMR δ_C ppm: 15.29 (CH_3, CH_3-14, CH_3-23), 24.51 (CH_2, C-10, C-27), 28.02 (CH_2, C-12, C-25), 28.42 (CH_2, C-11, C-26), 33.47 (CH_2, C-9, C-28), 40.15 (CH_2, C-13, C-24), 63.38 (CH_2, C-2, C-6), 69.51 (CH_2, C-3, C-5), 72.59 (CH, C-18, C-19), 159.13 (C, C-14, C-23), 169.11 (C, C-17, C-20), 173.23 (C, C-8, C-29).



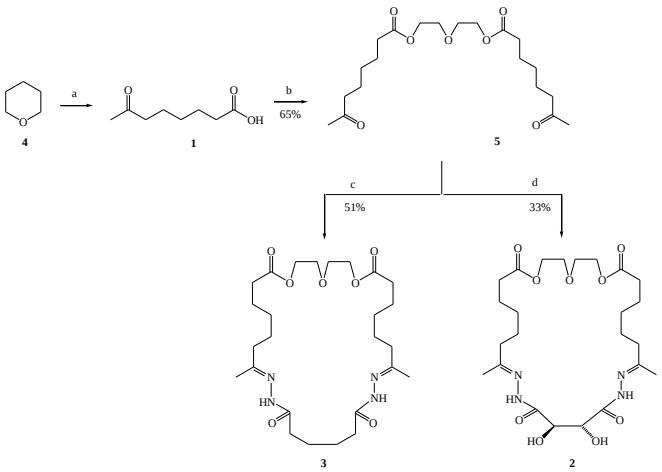
(14E,24E)-14,25-Dimethyl-1,4,7-trioxa-15,16,23,24-tetraazacyclogentriaconta-14,24-diene-8,17,22,31-tetraone ***(3)***. Yield: 0.67 g (51 %), yellowish thick oily liquid. *m/z* (APCI) %: 525.4 (100.0) $[M+H]^+$, 559.3 (100.0) $[M-H+Cl]^-$. $C_{26}H_{44}N_4O_7$. Calculated: [524.65]. IR (KBr) ν_{max} cm^{-1}: 1654 (CN), 1733 (OC(O)), 3320 (NH). ^{1}H NMR ($CDCl_3$) δ_H ppm: 0.85–0.97 (4H, m, H-11, H-28), 1.48–1.62 (12H, m, H-10, H-12, H-19, H-20, H-27, H-29), 1.76 (6H, s, CH_3-14, CH_3-25), 2.33 (4H, t J = 7.4 Hz, H-9, H-30), 2.38 (4H, t J = 7.0 Hz, H-13, H-26), 2.69 (4H, t J = 6.9 Hz, H-18, H-21), 3.53 (4H, t J = 6.0 Hz, H-3, H-5), 4.13 (4H, t J = 6.0 Hz, H-2, H-6), 8.66 (2H, br.s, NH). ^{13}C NMR δ_C ppm: 15.20 (CH_3, CH_3-14, CH_3-25), 24.00 (CH_2, C-19, C-20), 24.50 (CH_2, C-10, C-29), 25.63 (CH_2, C-12, C-27), 28.40 (CH_2, C-11, C-28), 28.80 (CH_2, C-18, C-21), 33.45 (CH_2, C-9, C-30), 40.11 (CH_2, C-13, C-26), 63.37 (CH_2, C-2, C-6), 69.50 (CH_2, C-3, C-5), 158.80 (C, C-14, C-25), 167.60 (C, C-17, C-22), 173.22 (C, C-8, C-31).

Results and Discussion

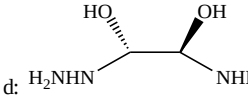
The aim of this work is the synthesis of two potentially useful 29- (**2**) and 31- (**3**) -membered macroheterocycles containing two ester groups each and including a crown ether fragment (diethylene glycol residue) and dihydrazide fragments of adipic and L-(+)-tartaric acids.

The choice of these groups was not random. Macrocyclic crown compounds and their acyclic analogs are capable of selective complex formation with metal cations, which allows them to be widely used in analytical chemistry (in optical, electrochemical methods of analysis, as well as methods of separation and concentration (extraction, sorption, chromatography, capillary electrophoresis and electrochromatography).[26] Adipic acid dihydrazide is used for crosslinking water-based emulsions, as well as as a hardener for some epoxy resins. Tartaric acid and its acyclic derivatives (esters, hydrazides, 1,3,4-oxadiazole-2-thions and 1,2,4-triazolthiol) are ideal ligands for creating strong colored organometallic complexes with ions Fe(III), Cu(II) и Ni(II),[27,28] they also have antibacterial and fungicidal activity. In addition, the macroheterocycle obtained by the reaction of [2+2]-cyclocondensation of L-(+)-tartaric acid dihydrazide with terephthalic aldehyde[29] is successfully used in the construction of synthetic chiral supramolecular compounds such as calix[N]arenes, cyclodextrins, crown esters, cucurbit[N]urils, *etc*. We assumed that other macrocyclic derivatives of L-tartaric acid dihydrazide would exhibit similar properties.

Synthesis of N- and O-containing macroheterocycles **2** and **3** included two stages. At the first of them, we carried out [2+1]-condensation of 7-oxooctanoic acid (**1**), obtained by the well-known method[1] from tetrahydropyran **4**, with diethylene glycol ditosylate. The yield of the obtained α,ω-diketodiester **5** did not exceed 65%, which is probably due to the reduced nucleophilicity of diethylene glycol. Subsequent [1+1]-interaction of diketone **5** with dihydrazides of L-(+)-tartaric and adipic acids at room temperature and high dilution (molar ratio: substrate:reagent:1,4-dioxane:water = = 1:1:100:100) leads to the formation of target macroheterocycles **2** and **3** with yields of 33 and 51 %, respectively. Such relatively low yields are probably explained by the reduced nucleophilicity of tartaric acid dihydrazide and the increased tendency to form linear condensation products due to the inclusion of crown ether fragments in their composition.



a: [1]; b: $O(CH_2CH_2OTs)_2$, K_2CO_3, MeCN, Δ;
c: $NH_2NHC(O)(CH_2)_4C(O)NHNH_2$, dioxane-$H_2O$;



d: , dioxane-H_2O.

The structure of the diketodiester **5** and macroheterocycles **2** and **3** was established by IR, 1H and 13C NMR spectroscopy. The NMR spectra of compounds **2** and **3** were analyzed by comparison with those of the starting diketodiester **5** and dicarboxylic acid hydrazides.

The absence in the IR spectra of reaction products **2** and **3** of an absorption band at 1716 cm^{-1} corresponding to the C=O groups of the initial diketodiester **5**, and the presence of such for the NH groups [3342 cm^{-1} (**2**) and 3320 cm^{-1} (**3**)] and C=N [1653 cm^{-1} (**2**) and 1654 cm^{-1} (**3**)] indicate the formation of a hydrazide fragment. In the ^{13}C NMR spectra of the reaction products **2** and **3** there are no signals of car-

bonyl carbon atoms [208.86 ppm], and in the ^{1}H NMR spectrum there are no signals of [~4.8 ppm] hydrazine (NH_2NH) fragment. These facts indicate that the resulting compounds are not linear substitution products. In the ^{13}C NMR spectra of compounds **2** and **3**, in addition to the signals of the carbon atom of the ester groups [173.23 ppm – in (**2**) and 173.22 ppm – in (**3**)] and the signals of the carbon atoms of the NH-C=O groups [167.11 ppm – in (**2**) and 173.22 ppm – in (**3**)], there are singlet signals of the C=N group [159.13 ppm – in (**2**) and 158.80 ppm – in (**3**)] and two quartets of CH_3 groups [15.29 ppm - in (**2**) and 15.20 ppm – in (**3**)], whose chemical shifts correspond to carbon atoms of two magnetically equivalent CH_3–C=N groups, which confirms the formation of a hydrazide (CH_2C=N-NH-C=O) grouping.

In the ^{1}H NMR spectra of the reaction products (**2**) and (**3**), there are no proton signals of the hydrazine (NH_2NH) residue [~4.8 ppm] and there are weak-field signals [9.61 ppm - in (**2**) and 8.66 ppm - in (**3**)], the magnitude of chemical shifts and integral intensities of which correspond to two protons of NHC=O groups of macrocycles. All these spectral data indicate the formation of macrocycles (**2**) and (**3**), which is further confirmed by the data of the APCI mass spectra, where protonated and deprotonated ions were clearly recorded.

Conclusions

Based on the available 7-oxooctanoic acid, we have carried out effective syntheses of two potentially useful 29- and 31-membered macrolides with fragments of diethylene glycol and dihydrazides of L-(+)-tartaric and adipic acids.

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