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SYNTHESIS OF MACROLIDES WITH *N*-CONTAINING (AZINE OR HYDRAZIDE) GROUPS

G. Yu. Ishmuratov,* M. P. Yakovleva, G. R. Mingaleeva,
R. R. Muslukhov, E. M. Vyrypaev, E. G. Galkin,
S. P. Ivanov, and A. G. Tolstikov

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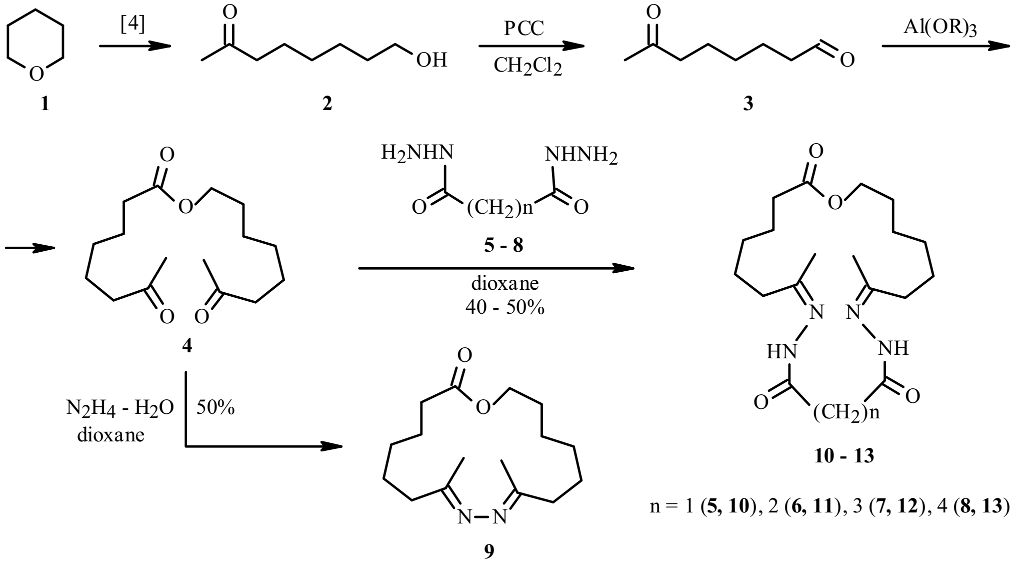
Potentially useful 17-, and 22÷25-membered macrolides containing azine or hydrazide groups were synthesized from tetrahydropyran via [1+1]-condensation at room temperature of 7-oxooctyl-7-oxooctanoate, which was obtained via Tishchenko reaction from 7-oxooctanal, with hydrazine hydrate and hydrazides of several dicarboxylic acids.

Key words: tetrahydropyran, 7-oxooctyl-7-oxooctanoate, macrolide, azine, hydrazide, synthesis.

Polyfunctional macroheterocycles with interesting complexing properties and biological activity are widely used as interphase-transfer catalysts, extractants, analytical reagents, and materials for creating ion-selective electrodes [1–3].

Herein we report the synthesis of 17- (**9**), 22- (**10**), 23- (**11**), 24- (**12**), and 25-membered (**13**) macrolides that may exhibit complexing properties and biological activity and contain azine or hydrazide functional groups. The synthetic scheme is based on chemo- and regioselective transformations of a ketoalcohol (**2**) that is accessible in three steps from tetrahydropyran (**1**) [4]. Corey oxidation of **2** produced ketoaldehyde **3**, which has been used to synthesize 9-oxo-2*E*-decenoic acid (multifunctional pheromone of honeybee *Apis mellifera* L.) [5], and small quantities (up to 15%) of 7-oxooctyl-7-oxooctanoate (**4**) by disproportionation of **3** via a Tishchenko reaction. The yield of **4** could be increased (up to 70%) by using the classical method [6] with catalytic quantities of aluminium triisopropoxide. [1+1]-Condensation of **4** in dioxane at high dilution and room temperature with hydrazine hydrate or dihydrazides of malonic (**5**), succinic (**6**), glutaric (**7**), and adipic (**8**) acids and subsequent successive work up of the reaction mixture with CH_2Cl_2 and hexane (1:10 ratio) produced in good yields (40–50%) macrolides with azine (**9**) or hydrazide (**10**–**13**) groups, respectively.



n = 1 (**5, 10**), 2 (**6, 11**), 3 (**7, 12**), 4 (**8, 13**)

Institute of Organic Chemistry, Ufa Scientific Center, Russian Academy of Sciences, Russian Federation, 450054, Ufa, prosp. Oktyabrya, 71, fax: 3472 35 60 66, e-mail: insect@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 395–399, July–August, 2009. Original article submitted February 6, 2009.

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TABLE 1. ^{13}C NMR Spectra of Diketoester **4** and Macrocycles **9**–**13**

Compound	1	2	3	4	5	6	7	8	9	10	11
4	173.31	33.96	–	–	208.86	64.15	–	29.77	23.25, 23.51, 24.58, 25.62,	43.30	–
	s	t			208.99 s	t		q	28.33, 28.47, 28.82 all t	43.46 t	
9	172.29	37.93	42.49	160.28	–	63.55	–	15.77	25.25, 25.51, 25.74, 28.17,	–	–
	s	t	t	s		t		q	28.83, 33.44 all t		
10	173.15	38.59	42.75	152.31	170.71	63.98	33.61	15.70	24.49, 25.09, 25.79, 28.16,	40.28	–
	s	t	t	s	s	t	t	q	28.28, 28.77, all t	t	
11	171.74	38.27	43.01	151.93	174.91	63.73	33.54	14.92	25.23, 25.91, 26.11, 26.42,	29.38	–
	s	t	t	s	s	t	t	q	27.96, 28.48 all t	t	
12	173.44	38.26	43.05	151.84	175.49	63.38	33.76	16.30	24.45, 25.44, 28.42, 28.60,	30.04	18.58
	s	t	t	s	s	t	t	q	28.96, 29.34 all t	t	t
13	173.43	38.37	43.38	152.02	175.90	64.00	33.80	15.03	24.44, 25.71, 28.30, 28.71,	38.50	28.45
	s	t	t	s	s	t	t	q	28.90, 29.39 all t	t	t

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1 – COO; 2 – CH_2COO; 3 – $CH_2C{=}N$; 4 – C=N; 5 – C=O; 6 – CH_2O; 7 – CH_2CH_2O; 8 – CH_3; 9 – CH_2; 10 – $CH_2C{=}O$; 11 – $CH_2CH_2C{=}O$.

IR spectra of **9**–**13** lacked absorption band at 1718 cm^{-1} that is characteristic of the ketone of key intermediate **4**. The IR spectrum of **9** contained bands at 1661 cm^{-1} (C=N); of **10**–**13**, at 1639 (C=N), 1670-1700 (CONH), and 3326-3420 (NH). These proved that macrocycles with azine and hydrazide groups, respectively, had been formed.

Structures of the macrocycles were studied using ^{13}C NMR and PMR spectrometry. PMR spectra of **9**–**13** were analyzed by comparison with those of the starting compounds **4** and hydrazides of dicarboxylic acids **5**–**8**.

^{13}C NMR spectra of **9**–**13** lacked resonances for carbonyl C atoms (208.86 and 208.99 ppm) and two CH_3-groups (29.77 ppm). PMR spectra did not show resonances for $CH_2C{=}O$ (2.39 ppm) and CH_3 (2.09 ppm) of **4**. Furthermore, PMR spectra of **10**–**13** lacked resonances of the hydrazine group (NH_2NH) (~4.8 ppm). These facts indicated that the products were not linear substitution products.

The ^{13}C NMR spectrum of **9** had a resonance for the ester C atom at 172.29 ppm, a singlet for C=N (160.28 ppm), and a strong-field quartet for two CH_3 groups (15.77 ppm). This indicated that a macrocycle containing an azine group had formed.

In analogy with **9**, ^{13}C NMR spectra of **10**–**13** contained resonances for ester C atoms (173.15 ppm, **10**; 171.74, **11**, 173.44, **12**, and 173.43, **13**) and resonances of NH–C=O groups of the starting dihydrazides (170.79 ppm, **5**; 173.37, **6**; 171.89, **7**; 175.43, **8**) that were shifted (170.71 ppm, **10**; 174.91, **11**, 175.49, **12**, 175.90, **13**). There were also singlets for C=N (152.31 ppm, **10**, 151.93, **11**, 151.84, **12**, 152.02, **13**) and two quartets for CH_3 (15.70 ppm, **10**, 14.92, **11**, 16.30, **12**; 15.03, **13**), the chemical shifts of which corresponded to C atoms of two magnetically equivalent CH_3–C=N groups [7–9]. The appearance of triplets (42.49 ppm, **9**; 42.75, **10**, 43.01, **11**; 43.05, **12**; 43.38, **13**) for two $CH_2C{=}N$ groups also confirmed that the hydrazides ($CH_2C{=}N–NH–C{=}O$) had formed.

PMR spectra of **10**–**13** lacked resonances for hydrazine protons (NH_2NH) (~4.8 ppm) and showed weak-field resonances (8.00 ppm, **10**, 8.10, **11**, 8.16, **12**; 8.90, **13**), the chemical shifts and integrated intensities of which corresponded to two protons of NHC=O groups in the macrocycles. Strong-field shifts of the two CH_3 groups (15.70 ppm, **10**; 14.92, **11**; 16.30, **12**; 15.03, **13**) showed that both double bonds CH_3–C=N of the macrocycles (**10**–**13**) had the *trans*-configuration. Chemical shifts of two CH_3 groups (1.90 ppm, **10**; 2.15, **11**; 2.10, **12**; 1.88, **13**) also indicated that they had the *cis*-orientation. Therefore, the double bonds of macrocycles **10**–**13** had the *trans*-configuration. Tables 1–3 list the ^{13}C NMR and PMR spectra of the starting materials and products.

Resonances of C atoms of NHC=O groups in ^{13}C NMR spectra of **10**–**13** were noticeably broadened compared with those of the corresponding C atoms in starting dihydrazides **5**–**8**. This was probably related to tautomeric conversions in the macrocycles.

All these spectral data indicated that macrocycles **9**–**13** had formed. This was also confirmed by mass spectra.

TABLE 2. PMR Spectra of Diketoester **4** and Macrocycles **9**–**13**

Compound	CH_3	-CH_2-	$CH_2C=N$	CH_2COO	CH_2O	$CH_2C=O$	$\underline{CH_2}CH_2C=O$	NH
4	2.09 s	1.30–1.54 m	–	2.24 t	4.00 t	2.39 t	–	–
9	2.02 s	1.20–1.50 m	2.08 t	2.46 t	4.02 t	–	–	–
10	1.90 s	1.10–1.40 m, 1.40–1.60 m	2.15 t	2.40 t	4.05 t	2.25 s	–	8.00 br.s
11	2.15 s	1.40–1.80 m	2.28 t	2.35 t	4.05 t	2.67 s	–	8.10 br.s
12	2.10 s	1.20–1.40 m, 1.40–1.70 m	2.20 t	2.51 t	3.90 t	2.30 t	1.95 t	8.16 br.s
13	1.88 s	1.20–1.40 m, 1.40–1.70 m	2.25 t	2.52 t	4.10 t	2.35 t	1.80 t	8.90 br.s

TABLE 3. ^{13}C NMR and PMR Spectra of Dihydrazides **5**–**8**

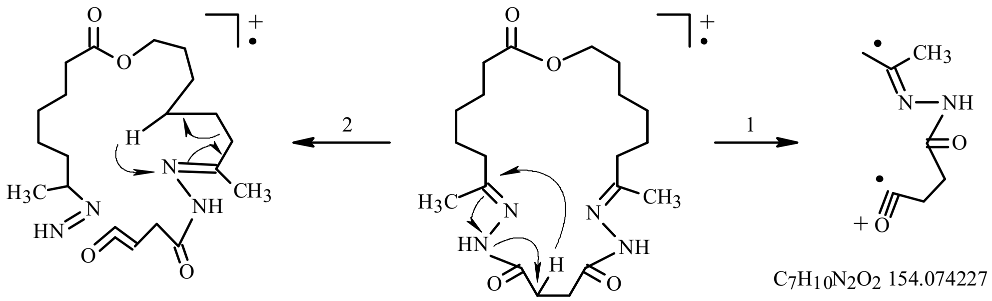
Compound	δ_C			δ_H		
	C=O	$\underline{C}H_2C=O$	$\underline{C}H_2CH_2=O$	$CH_2C=O$	$\underline{C}H_2CH_2C=O$	NH_2-NH(+H_2O)
5	170.79 s	42.47 t	–	3.25 s	–	4.75 br.s
6	173.37 s	29.03 t	–	2.52 s	–	4.75 br.s
7	171.89 s	30.04 t	18.58 t	2.31 t	1.95 t	4.90 br.s
8	175.43 s	37.81 t	28.83 t	2.30 t	1.70 t	4.80 br.s

Macrocycles **9**–**13** were studied using atmospheric pressure chemical ionization (APCI) with detection of positive and negative ions (20 eV) and using electron-impact ionization (EI, 70 eV).

Because the macrocycles were highly unstable adducts, especially under the high-vacuum conditions used for mass spectrometry, the APCI spectra of **9**–**13** were obtained first. Very strong peaks of protonated MH$^+$ and deprotonated [M – H]$^-$ ions and those of ionic associates with 1÷3 water molecules were detected. The ability for protonation and solvation by water is well known in the chemistry of amides and hydrazides [10]. This dictated the initial study using APCI.

The EI mass spectrum of **11**, which contained an ester and two C=NNHC=O groups separated by two methylene units, was obtained in order to confirm the elemental composition and structures of **9**–**13**. Mass spectra of dihydrazide **6** from a commercial source and synthesized by us was used as a reference.

The molecular ions (MI) could exist as the cyclic or open forms according to the intensities of the peaks for the MI. Because the MI of **11** [M]$^+$ = 394.255 ($C_{19}H_{30}N_4O_4$, calc. 394.2580) was weak (1% of the base peak), it was obvious that it existed exclusively in the open form/forms. Functional groups capable of intramolecular protonation (carbonyl, amide, imine) faciliated opening of the ring. H atoms could migrate by the standard mechanism through 4- and 6-membered transition states (MacLafferty rearrangement) and due to the presence of rather long and conformationally flexible polymethylene chains through nonspecific migration of H atoms upon approach to potential proton acceptors [11]. It is thought [12] that these are H atoms located mainly in the *α*-position to other functional groups. Keto—enol tautomerism processes that can stabilize the MI and enhance new decomposition pathways can compete with these processes.



The MI of **11** typically fragmented at the N–C(O) and C–C bonds in the β-position to the double bonds. As a result, one of the main fragments had *m*/*z* 154.05 ($C_7H_{10}N_2O_2$, measured 154.0742). It was produced through two simple β-cleavages (1) or via ring opening and subsequent cleavage via two successive MacLafferty rearrangements (2) [11].

The EI mass spectrum of **11** also showed fragments $[M – 16]^+$, $[M – 71]^+$, and $[M – 113]^+$ that corresponded to loss of NH_2, $C_3H_7N_2$, and $C_3H_7N_2COCH_2$. The peak for the $[C_3H_8N_2]$ ion (measured 72.060; calc., 72.0687) was the base peak in its spectrum.

We decided to limit the examination to peaks that confirmed the structures and molecular weights because of the complexity of the mass spectra of **10**, **12**, and **13** and the accurately measured values for most of the peaks in the APCI and EI mass spectra of **11**. It was assumed that the main fragments of model spectra would be observed and that decomposition of the MI of the products would greatly simplify the interpretation of their mass spectra. Thus, the mass spectrum of **11** exhibited fragments with *m*/*z* 141.0939 that corresponded to $[C_8H_{13}O_2]$. The ion of this composition was one of the main ones in the spectrum of starting diketoester **4** and obviously had the structure $[CH_3–C(=O)C_5H_{10}–C=O]^+$. However, it was formed in **11** by other atoms of the macrocycle and presumably had the structure $[CH_2=CH–C(=O)–OC_4H_8]^+$ or $[CH_2–CH=CH(OH)–OC_3H_6CH=CH_2]^+$, i.e., through-space migration of the α-H atom (relative to the ester carbonyl) to the N atom with subsequent β-cleavage relative to the double bond or possibly MacLafferty rearrangement and keto–enol rearrangement in the ester part of the ring was necessary.

Thus, the mass spectrometric study of **9**–**13** led to the following conclusions. Because peaks of protonated positive MH^+ and deprotonated negative $[M – H]^–$ ions were detected in APCI spectra of the whole series **9**–**13**, the appearance of this tendency could be considered proof of the existence of compounds with the corresponding molecular weights. The EI mass spectrum of **11** with exact measurement of MI peaks confirmed that it had the proposed empirical formula.

EXPERIMENTAL

IR spectra in thin layers were recorded on a UR-20 instrument. NMR spectra in $CDCl_3$ and DMSO-d_6 with TMS internal standard and in D_2O with DSS internal standard were recorded on a Bruker AM-300 spectrometer (operating frequency 300.13 MHz for ^1H; 75.47, ^{13}C). Chromatography was performed in Chrom-5 [column length 1.2 m, stationary phase SE-30 (5%) silicone on Chromaton N-AW-DMCS (0.16–0.20 μm), operating temperature 50–300°C] and Chrom-41 [column length 2.4 m; stationary phase PEG-6000, operating temperature 50–200°C] instruments with He carrier gas. Column chromatography used SiO_2 (70–230, Lancaster, England); TLC, Sorbfil SiO_2 (Russia). Elemental analyses of all compounds agreed with those calculated. The mass spectrum of **11** was obtained in a Finnigan MAT 95 XL instrument with DEC Alpha Station 433 au data processing system at source temperature 250°C and ionizing electron energy 70 eV. Samples were introduced through an HP–GC 6890. Exact masses were determined in the range 1–3,500 Da with 50,000 resolution. Mass spectra of **9**–**13** were recorded on a Shimadzu LCMS 2010 EV instrument under APCI conditions at electron energy 20 eV with detection of positive and negative ions. The mobile phase was water and CH_3CN at flow rates 0.02 mL/min.

7-Oxooctanal (3). A suspension of pyridinium chlorochromate (7.33 g, 34.0 mmol) in anhydrous CH_2Cl_2 (92 mL) was stirred (20°C, Ar), treated with a solution of **2** (3.30 g, 22.7 mmol) obtained from tetrahydropyran (**1**) [4] in CH_2Cl_2 (55 mL), stirred for 2 h at room temperature, diluted with Et_2O (200 mL), and filtered through a layer of SiO_2. The filtrate was evaporated to afford **3** (2.14 g, 65%). The IR and NMR spectra were identical with those published [13].

7-Oxooctyl-7-oxooctanoate (4). A solution of **3** (0.50 g, 4.0 mmol) in petroleum ether (5 mL) was treated at room temperature with aluminium triisopropoxide (0.05 g, 0.2 mmol) and stirred for 48 h. The solvent was evaporated. The solid was chromatographed (SiO_2, petroleum ether—Et_2O, 7:3, R_f 0.18) to afford **4** (0.80 g, 70%). The IR and NMR spectra were identical to those published [13].

8,11-Dimethyl-1-oxa-9,10-diaza-8,10-cycloheptadecadien-2-one (9). Diketoester **4** (0.28 g, 1.0 mmol) in anhydrous dioxane (30 mL) was stirred vigorously, treated slowly dropwise with hydrazine hydrate (0.51 g, 1.0 mmol), and stirred for 48 h (TLC monitoring). The dioxane was evaporated at reduced pressure. The solid was dissolved in CH_2Cl_2 (20 mL), washed with water (3 × 5 mL), and dried over $MgSO_4$. The solvent was evaporated. The resulting solid was treated with stirring successively with anhydrous CH_2Cl_2 (1 mL) and hexane (10 mL). The layers were allowed to separate. The upper layer was decanted. The remainder was washed with hexane (5 mL) and evaporated in vacuo to afford **9** (0.11 g, 40%).

APCI mass spectrum (20 eV, MW, ion type, *m/z*): M = 280; MH^+ 281; $[MH + H_2O]^+$ 299; $[MH + 2H_2O]^+$ 317; negative ions: $[M - H]^-$ 279; $[M + H_2O - H]^-$ 297.

General Method for Preparing Macrocycles. Diketoester **4** (0.28 g, 1.0 mmol) in anhydrous dioxane (30 mL) was stirred vigorously, treated with the dihydrazide of the appropriate dicarboxylic acid (1.0 mmol, **5**, **6**, **7**, or **8**) prepared by the literature method [14], and stirred for 48 h (TLC monitoring for disappearance of **4**). Dioxane was evaporated at reduced pressure. The solid was dissolved in CH_2Cl_2 (20 mL), washed with water (3 × 5 mL), and dried over $MgSO_4$. The solvent was evaporated. The resulting solid was treated with stirring with anhydrous CH_2Cl_2 (1 mL) and hexane (10 mL). The layers were allowed to separate. The upper layer was decanted. The remainder was washed with hexane (5 mL) and evaporated in vacuo.

8,16-Dimethyl-1-oxa-9,10,14,15-tetraaza-8,15-cyclodocosadien-2,11,13-trione (10). Yield 0.16 g (44%). APCI mass spectrum (20 eV, MW, ion type, *m/z*): MH^+ 381; negative ions $[M - H]^-$ 379, $[M + H_2O - H]^-$ 397.

8,17-Dimethyl-1-oxa-9,10,15,16-tetraaza-8,16-cyclotricosadien-2,11,14-trione (11). Yield 0.18 g (46%). Mass spectrum [EI, ion type, measured accurate mass number (% of base peak), elemental formula, calculated accurate mass number]: M^+ 394.2550 (1.0, $C_{20}H_{34}N_4O_4$, 394.2580), $[M - C_3H_7N_2]^+$ 323.1680 (13.8, $C_{17}H_{27}N_2O_4$, 323.1845), 281 (13.8), 167 (15.5), 154 (51.4), 114 (33.0), 86 (26.0), 72.06 (100, $C_3H_8N_2$, 72.0687). APCI mass spectrum (20 eV, ion type, *m/z*): MH^+ 395, $[MH + H_2O]^+$ 413; negative ions: $[M - H]^-$ 393, $[M + H_2O - H]^-$ 411.

8,18-Dimethyl-1-oxa-9,10,16,17-tetraaza-8,17-cyclotetracosadien-2,11,15-trione (12). Yield 0.17 g (42%). APCI mass spectrum (20 eV, ion type, *m/z*): MH^+ 409; $[MH + H_2O]^+$ 427; negative ions: $[M - H]^-$ 407; $[M + H_2O - H]^-$ 425; $[M + 2H_2O - H]^-$ 443.

8,19-Dimethyl-1-oxa-9,10,17,18-tetraaza-8,18-cyclopentacosadien-2,11,16-trione (13). Yield 0.20 g (47%). APCI mass spectrum (20 eV, ion type, *m/z*): MH^+ 423; $[MH + H_2O]^+$ 441; negative ions: $[M - H]^-$ 421; $[M + H_2O - H]^-$ 439; $[M + 2H_2O - H]^-$ 457.

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