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MACROCYCLIC LACTONIZATION OF 3*R*,7-DIMETHYL-6*S*-HYDROXYOCTANOIC ACID

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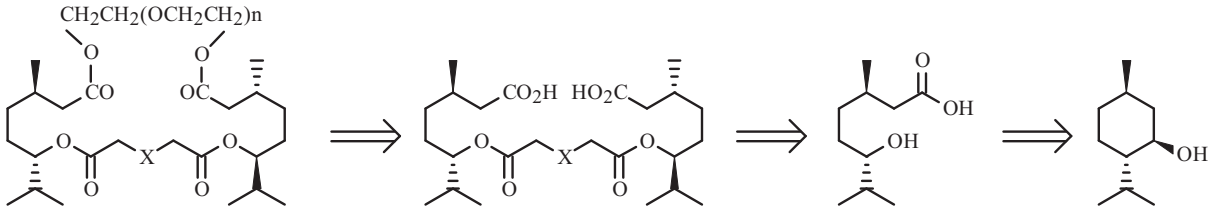
*A mixture of cyclic lactones [7- (mentholactone), 14-, 21-, 28-, and 35-membered polylactones] instead of the expected [2 + 1]-condensation products was obtained from the reaction of 3*R*,7-dimethyl-6*S*-hydroxyoctanoic acid, which is accessible from l-menthol, and glutaric, adipic, and bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid dichlorides in Py in the presence of* N,N-*dimethylaminopyridine. The structures were confirmed using PMR, ^{13}C NMR, and mass spectra.*

Keywords: l-menthol, 3*R*,7-dimethyl-6*S*-hydroxyoctanoic acid, dicarboxylic acid dichlorides, pyridine, *N*,*N*-dimethylaminopyridine.

Crown ethers are macroheterocycles containing greater than 11 atoms, of which at least four are heteroatoms, linked by ethylene bridges [1].

Hybrid structures **1** with chiral centers and crown-ether segments were supposed to be synthesized via sequential [2 + 1]-condensation of several diacid dichlorides with 3*R*,7-dimethyl-6*S*-hydroxyoctanoic acid (**3**) and [1 + 1]-condensation of intermediate diacids **2** with polyethylene glycols.



1 **2a-c** **3** **4**

n = 0, 1, 2

X = CH_2 (**2a**); $(CH_2)_2$ (**2b**); (**2c**)

Previously, optically active macroheterocycle **5** with two esters and a diacylhydrazine moiety was prepared from l-menthol (**4**) [2]. The first synthetic step was [2 + 1]-condensation of glutaric acid dichloride with methyl 3*R*,7-dimethyl-6*S*-hydroxyoctanoate [3].

Attempts to perform the [2 + 1]-condensation with dichlorides of several diacids (glutaric, adipic, and bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acids) and **3** under the conditions reported for isosteviol [4] with a deficiency of Py and DMAP catalyst were unsuccessful. Expected diacids **2a**–**c** with two esters did not form according to a single O=CO resonance in the ^{13}C NMR spectrum near 175.00 ppm that was shifted compared to that of starting **3** (177.84 ppm). Also, this region for products **2a**–**c** would have two resonances (carboxylic acid and ester). In all instances, the same product mixture was obtained (according to spectral data). The mixture did not contain starting acid **3** [^{13}C NMR spectrum, 76.73 ppm,

†Deceased.

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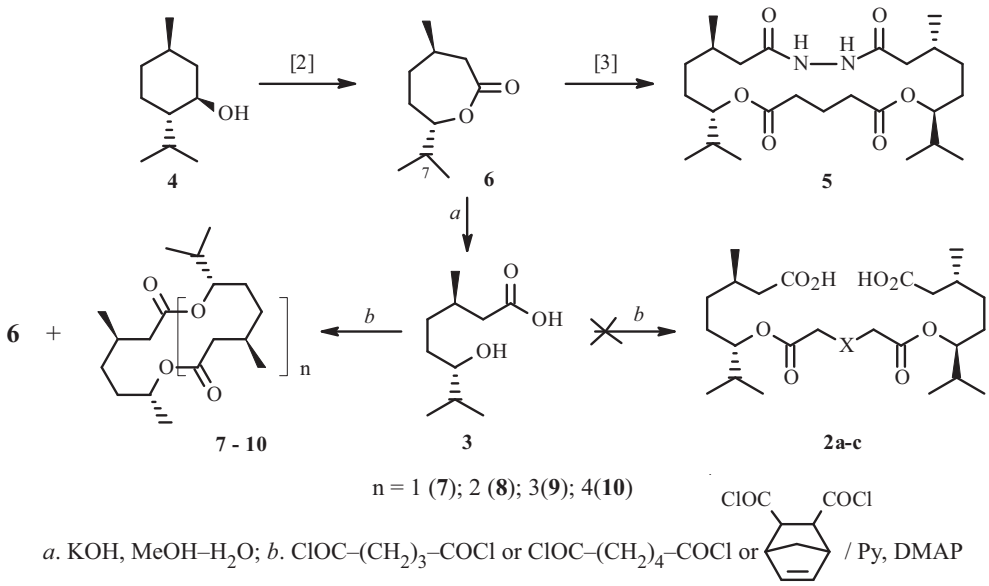
(CH–OH); PMR spectrum, 6.50 br.s, (OH); IR spectrum, 3375 cm^{-1} (OH)], target diacids **2a**–**c**, and linear condensation products of polyesters with carboxylic acids on the ends of the chain as indicated by no evidence for them in the spectra and the absorption band at 1716 cm^{-1} characteristic of –COOH that was shifted to 1730 (ester C=O). IR, PMR, and ^{13}C NMR spectra of the reaction products were identical to those of (–)-mentholactone (**6**) [3, 5], suggesting with high probability that it was present. Chromatography of the reaction products over various columns also indicated that only **6** was present. However, APCI mass spectra (MeCN, MeCN–H_2O) detected consistently peaks for $[M + H]^+$ with *m*/*z* 171.05, 341.30, 511.45, 681.60, and 851.90 that corresponded to mono- (**6**), di- (**7**), tri- (**8**), tetra- (**9**), and pentalactones (**10**) and for $[M + H_2O + H]^+$ with *m*/*z* 359.30, 529.50, 699.65, and 869.90 of lactones **7**–**10**. The intensities of the last set decreased on going to pure MeCN and increased if the retention time increased. Monolactone **6** (*m*/*z* 169.10) and its hydrated ion (*m*/*z* 187.15) were also analyzed in negative-ion mode.



The mass spectrum of starting **3** (*m*/*z* 188.26) was recorded under the same conditions to exclude the possibility that polylactones **7**–**10** formed from **3** under the analytical conditions. Peaks of polylactones were not detected.

The results led to the conclusion that **3** in Py in the presence of dicarboxylic acid dichlorides and *N*,*N*-dimethylaminopyridine (DMAP) formed a mixture of 7-membered mentholactone (**6**), 14-membered **7**, 21-membered **8**, 28-membered **9**, and 35-membered **10**. This mixture still cannot be separated. Other products were not observed using GC, probably because they were unstable under the analytical conditions. Catalysis by DMAP hydrochloride similar to that observed for ricinoleic acid [6] or the similar Yamaguchi esterification [7] may have formed the mixture of **6**–**10** through formation of mixed anhydrides of **3** and the dicarboxylic acid dichlorides. An experiment without the diacid dichlorides where lactones were not detected argued in favor of this.

Only monolactone **6** formed with an excess of Py according to APCI mass spectra (Scan+) with $[M + H]^+$ 171.05 and $[M + H + MeCN]^+$ 212.05. $C_{10}H_{18}O_2$ (170.2487).

EXPERIMENTAL

Equipment of Khimiya Common Use Center, UfIC, RAS, was used in the work. IR spectra were recorded from thin layers on a Prestige-21 FTIR (Shimadzu). NMR spectra were recorded in $CDCl_3$ with TMS internal standard on a Bruker AM-500 spectrometer (operating frequency 500.13 MHz for ^1H and 126.76 MHz for ^{13}C). Chromatographic analysis used Chrom-5 [column length 1.2 m, stationary phase SE-30 silicone (5%) on Chromaton N-AW-DMCS (0.16–0.20 mm), operating temperature 50–300°C] and GC-9A instruments (quartz capillary column length 25 m, stationary phase OV-101, operating temperature 80–280°C; Shimadzu) and He carrier gas. APCI mass spectra were taken on an LCMS 2010 EV (Shimadzu) at electron energy 20 eV in positive- and negative-ion modes. The mobile phase was H_2O–MeCN (25:75) or MeCN at flow rate 0.1 mL/min and retention times for Scan(C+): 1.100 > 1.200–1.050 min, 1.100 > 1.200–1.500 min, 1.200 > 1.300–1.100 min, 1.200 > 1.300–1.050 min, 1.200 > 1.300–1.500 min, 1.250 > 1.350–1.150 min, 1.250 > 1.350–0.900 > 3.725 min,

1.250 > 1.350–1.550 min and for Scan(C–): 1.125 > 1.225–1.075 min, 1.125 > 1.225–1.525 min, 1.225 > 1.325–1.125 min, 1.225 > 1.325–1.075 < > 3.325 min, 1.250 > 1.350–1.150 min, 1.250 > 1.350–1.550 min. TLC monitoring used Sorbfil SiO_2 (Russia). l-Menthol (optical purity 100%) was isolated from mint oil as before [8].

3*R*,7-Dimethyloctan-6*S*-olide (6) was prepared according to the literature [5], R_f 0.74 (PE–MTBE, 2:1). $[\alpha]_D^{20}$ –26.5° (*c* 2.9, $CHCl_3$). IR spectrum (KBr, ν, cm^{-1}): 1730 (O=C–O), 1390, 1380 (CH_3). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.87, 0.89 and 0.94 (9H, d, J = 6.8, CH_3-3, 7), 1.21 (1H, dtd, J = 13.2, 11.8, 1.2, H_a-4), 1.49 (1H, dtd, J = 11.7, 11.8, 1.2, H_a-5), 1.70–1.92 (4H, m, H_a-3, H_e-4, H_e-5, H-7), 2.43 (1H, dd, J = 13.3, 1.9, H_e-2), 2.52 (1H, dd, J = 13.3, 10.9, H_a-2), 3.90 (1H, ddd, J = 9.2, 4.4, 0.9, H_a-6). ^{13}C NMR spectrum ($CDCl_3$, δ, ppm): 17.11 and 18.47 (CH_3, C-8, 9), 23.92 (CH_3, C-10), 30.42 (CH, C-3), 30.96 (CH_2, C-4), 33.33 (CH, C-7), 37.46 (CH_2, C-5), 42.58 (CH_2, C-2), 84.73 (CH, C-6), 175.00 (C, C-1). Mass spectrum (APCI, 20 eV), *m/z* ($I_{rel.}$, %) found: (Scan+): 171.05 $[M + H]^+$, 212.15 $[M + H + MeCN]^+$; (Scan–): 169.10 $[M – H]^–$, 187.15 $[M – H + H_2O]^–$. Calcd for $C_{10}H_{18}O_2$, 170.2487.

3*R*,7-Dimethyl-6*S*-hydroxyoctanoic Acid (3). A solution of mentholactone (**6**, 4.49 g, 26.4 mmol) in MeOH (25 mL) at room temperature was stirred vigorously, treated with KOH (2.28 g, 40.7 mmol), and stored for 6 h (TLC monitoring). The excess of MeOH was distilled at reduced pressure. The residue was diluted with H_2O (50 mL), washed with CH_2Cl_2 (3 × 5 mL), acidified with HCl to pH 5, and extracted with CH_2Cl_2 (50 mL). The extract was washed with NaCl solution (3 × 5 mL), dried over $MgSO_4$, and evaporated to afford **3** (4.75 g, 96%). R_f 0.12 (PE–MTBE 2:1). $[\alpha]_D^{20}$ +1.40° (*c* 1.88, CH_2Cl_2). IR spectrum (KBr, ν, cm^{-1}): 3319 (OH), 1716, 1458 (COOH). ^1H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84 and 0.86 (6H, d, J = 6.9, CH_3-7), 0.92 (3H, d, J = 6.6, CH_3-3), 1.25–1.35 (2H, m, H-4), 1.43–1.57 (2H, m, H-5), 1.78 (1H, m, H-7), 1.85–1.94 (1H, m, H-3), 2.05 (2H, d, J = 8.0, H-2), 4.01 (1H, m, H-6), 6.49 (2H, br.s, OH). ^{13}C NMR spectrum (127 MHz, $CDCl_3$, δ, ppm): 17.06 (CH_3, CH_3-3), 18.77 and 19.73 (CH_3, CH_3-7, C-8), 30.24 (CH, C-3), 31.02 (CH_2, C-4), 32.85 (CH_2, C-5), 33.14 (CH, C-7), 41.35 (CH_2, C-2), 76.73 (CH, C-6), 177.84 (C, C-1). Mass spectrum (APCI, 20 eV), *m/z* (I_{rel}, %) found: Scan (–): 187.05 (100.00) $[M – H]^–$. Calcd for $C_{10}H_{20}O_3$, 188.2640.

Reaction of 3*R*,7-Dimethyl-6*S*-hydroxyoctanoic Acid and Glutaric, Adipic, and Bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic Acid Dichlorides: *a) with a deficiency of Py*. A cold (0°C) solution of **3** (2.00 g, 10.6 mmol) and DMAP (0.05 g, 0.4 mmol) in anhydrous CH_2Cl_2 (50 mL) under Ar was stirred vigorously, treated sequentially with Py (0.22 g, 0.23 mL, 2.9 mmol) and the dichloride of the appropriate acid (5.3 mmol) in anhydrous CH_2Cl_2 (5 mL), stirred for 24 h, and washed with acidified H_2O (3 × 10 mL) and NaCl solution (3 × 10 mL). The organic layer was dried over $MgSO_4$ and evaporated at reduced pressure to afford a mixture (1.94–2.00 g) of lactones **6**–**10**;

b) with an excess of Py. A cold (0°C) solution of **3** (1.00 g, 5.3 mmol) and DMAP (0.03 g, 0.2 mmol) in anhydrous Py (1.7 mL, 21.0 mmol) under Ar was stirred vigorously, treated with adipic acid dichloride (0.48 g, 2.7 mmol) that was prepared as before [9], diluted with CH_2Cl_2 (50 mL), stirred for 24 h, and washed with acidified H_2O (3 × 10 mL) and NaCl solution (3 × 10 mL). The organic layer was dried over $MgSO_4$ and evaporated at reduced pressure to afford **6** (0.63 g, 70%).

(4*R*,7*S*,11*R*,14*S*)-7,14-Diisopropyl-4,11-dimethyl-1,8-dioxacyclotetradecane-2,9-dione (7). Mass spectrum (APCI, 20 eV), *m/z* (I_{rel}, %): (Scan+): 341.30 $[M + H]^+$, 359.30 $[M + H + H_2O]^+$; (Scan–): 339.35 $[M – H]^–$, 357.35 $[M – H + H_2O]^–$. Calcd for $C_{20}H_{36}O_4$, 340.4974.

(4*R*,7*S*,11*R*,14*S*,18*R*,21*S*)-7,14,21-Triisopropyl-4,11,18-trimethyl-1,8,15-trioxacycloheneicosane-2,9,16-trione (8). Mass spectrum (APCI, 20 eV), *m/z* (I_{rel}, %): (Scan+): 511.45 $[M + H]^+$, 529.50 (100.00) $[M + H + H_2O]^+$; (Scan–): 509.55 $[M – H]^–$, 527 $[M – H + H_2O]^–$. Calcd for $C_{30}H_{54}O_6$, 510.7400.

(4*R*,7*S*,11*R*,14*S*,18*R*,21*S*,25*R*,28*S*)-7,14,21,28-Tetraisopropyl-4,11,18,25-tetramethyl-1,8,15,22-tetraoxacyclooctacosane-2,9,16,23-tetraone (9). Mass spectrum (APCI, 20 eV), *m/z* (I_{rel}, %): (Scan+): 681.60 $[M + H]^+$, 699.90 $[M + H + H_2O]^+$, 717.70 $[M + H + 2H_2O]^+$; (Scan–): 679.80 $[M – H]^–$, 697.70 $[M – H + H_2O]^–$. Calcd for $C_{40}H_{72}O_8$, 680.9948.

(4*R*,7*S*,11*R*,14*S*,18*R*,21*S*,25*R*,28*S*,32*R*,35*S*)-7,14,21,28,35-Pentaisopropyl-4,11,18,25,32-pentamethyl-1,8,15,22,30-pentaoxacyclopentatriacontane-2,9,16,23,30-pentaone (10). Mass spectrum (APCI, 20 eV), *m/z* (I_{rel}, %): (Scan+): 851.90 $[M + H]^+$, 869.90 $[M + H + H_2O]^+$, 887.95 $[M + H + 2H_2O]^+$; (Scan–): 849.50 $[M – H]^–$, 867.95 $[M – H + H_2O]^–$. Calcd for $C_{50}H_{90}O_{10}$, 850.

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