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Synthesis of Macrolides with Malonic Fragment and Products of C–Alkylation Reaction from Castor Oil

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The [1+1]-condensation reaction of natural castor oil (triglyceride of (R,Z)-(+)-12-hydroxy-9-octadecenoic acid) with malonic acid chloride was carried out by one-stage synthesis. Optically active macroheterocycles with four ester groups were obtained, their malonic fragment being additionally alkylated by 1-bromotridecane or 2-(8-bromooctyl) tetrahydro-2H-pyran.

Key words: Castor oil, macrolide, synthesis, malonic acid, *C*-alkylation reaction.

Синтез макролидов с малонатным фрагментом и продуктов его C–алкилирования из касторового масла

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Реакцией [1+1]-конденсации природного касторового масла (триглицерида (R,Z)-(+)-12-гидрокси-9-октадеценовой кислоты) с хлорангидридом малоновой кислоты осуществлен одностадийный синтез оптически активных макрогетероциклов с четырьмя сложноэфирными группами, дополнительно проалкилированных тридецил- или 1-тетрагидропиранилоксиокт-8-ил бромидами по малонатному фрагменту.

Ключевые слова: Касторовое масло, макролид, синтез, малоновая кислота, реакция *C*-алкилирования.

Introduction

Today, synthetic transformations of natural compounds are one of the world's leading trends in the creation of new drugs for medicine and agriculture. In this regard, theoretical and practical interest is the available compound of natural origin-castor oil extracted from the seeds of *Ricinus communis L.* Castor oil has found wide application[1] in industry, in medicine as a laxative or as a basis of ointments and balms (including Vishnevsky ointment), as well as in cosmetology as a means to strengthen hair and eyelashes. The presence of free hydroxyl functional groups in castor oil allows the introduction of additional pharmacophore (ester) groups, which can increase and/or change the existing biological activity. Another way of introducing additional functions into molecules of organic compounds is the *C*-alkylation reaction of the malonate fragment, which is widely used for the introduction of new C-C bonds,[2] in order to increase or decrease the hydrophilicity of the target molecules.

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_2O with TMS internal standard on a Bruker AM-500 spectrometer (operating frequency 500.13 MHz for ^1H, 126.76 MHz for ^{13}C). Mass spectra were recorded on a LC/MS 2010 EV Shimadzu instrument (syringe input, sample solution in CH_3CN 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_2O:CH_3CN (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. CH_2Cl_2, pyridine, *n*-heptane and DMF purified and dried according to standard methods[3] were used to perform the reactions and to separate the target compounds.

*13R,19R-Dihexyl-33-(2’-oxa-3’-oxo-14’R-hydroxyeicos-11’Z-en-1’-yl)-1,14,18,31-tetraoxa-2,15,17,30-tetraoxocyclotritricosa-10Z,21Z-diene (**2**) (and/or 13R,19R-dihexyl-33-(1’-oxa-2’-oxo-13’R-hydroxynonacos-10’Z-en-1’-yl)-1,14,18,31-tetraoxa-2,15,17,30-tetraoxocyclotetratricosa-10Z,21Z-diene (**2a**)).* Dry castor oil (**1**) (6.00 g, 6.4 mmol) and 0.08 g (0.6 mmol) DMAP in dry CH_2Cl_2 (41 mL) and dry Py (2 mL, 25.0 mmol) was added to the solution of fresh malonic acid chloride (1.08 g, 6.43 mmol) in dry CH_2Cl_2 (3 mL) with cooling to 0–5 °C in an inert atmosphere of argon. The reaction mixture was stirred for 8 hours at room temperature (TLC control), then diluted with CH_2Cl_2 (200 mL) and sequentially washed with 5 % HCl (3×10 mL), brine (3×10 mL), dried with $MgSO_4$ and evaporated. The sediment with *n*-heptane was decanted. Yield: 6.35 g (96 %) of macroheterocycles **2** and/or **2a**. R_f = 0.47 (*n*-hexane, MTBE 1:1). *m/z* $C_{60}H_{104}O_{11}$ (1001.4612) (ESI, Irelative, %): (Scan+): 1020.05 (0.48) $[M+H_2O+H]^+$, 1002.30 (0.14) $[M+H]^+$; Scan (C-): 1000.08 (0.08) $[M-H]^-$, 702.60 (40.39) $[M-C_{18}H_{34}O_3-H]^-$. IR (KBr) ν_{max} cm^{-1}: 1735, 1742 (C=O), 3520 (OH). ^1H NMR ($CDCl_3$) δ_H ppm: 0.83 (9H, t, *J* = 6.5 Hz, H-20’, 2H-6’’), 1.15–1.35 (54H, m, H-4÷H-8, H-24÷H-28, H-5’÷H-9’, H-16’÷H-19’, 2(H-2”÷H-5”)), 1.36–1.51 (6H, m, H-15’, 2H-1’’), 1.90–2.01 (6H, m, H-9, H-23, H-10’), 2.27 (6H, t, *J* = 7.3 Hz, H-3, H-16, H-29, H-4’), 3.13 (1H, br.s, OH), 3.50–3.61 (1H, m, H-14’), 4.05 (2H, t, *J* = 9.3 Hz, H-16), 4.20–4.29 (4H, m, H-32, H-1’), 4.80–4.90 (2H, m, H-13, H-19), 5.10–5.19 (1H, m, H-33), 5.20-5.51 (6H, m, H-10, H-11, H-21, H-22, H-11’, H-12’). ^{13}C NMR ($CDCl_3$) δ_C ppm: 14.03 (q, C-20’, C-6”), 22.57 (t, C-5’’, C-19’), 24.75, 25.17, 25.53, 25.64 (t, C-2’’, 4, 5’, 7, 10’, 16’, 25, 28), 26.87, 27.14, 27.31 (t, C-5, C-6, C-9, C-23, C-26, C-27) 28.98, 29.04, 29.07, 29.31, 29.46, 29.52, 29.64 (t, C-3’’, C-6’, C-7’, C-8, C-8’, C-9’, C-17’, C-24), 31.01, 31.66, 33.79 (t, C-4’’, C-12, C-13’, C-18’, C-20), 33.93 (t, C-3, C-29), 34.09 (t, C-4’) 35.22 (t, C-1’’), 36.70 (t, C-15’), 49.29 (t, C-16), 62.05 (t, C-1’, C-32), 68.84 (d, C-14’), 71.48 (d, C-33), 72.99 (d, C-13, C-19), 123.86 (d, C-11, C-21), 125.27 (d, C-12’), 132.67 (d, C-11’), 132.93 (d, C-10, C-22), 166.29 (s, C-15, C-17), 172.23, 172.82 (s, C-2, C-3’, C-30).

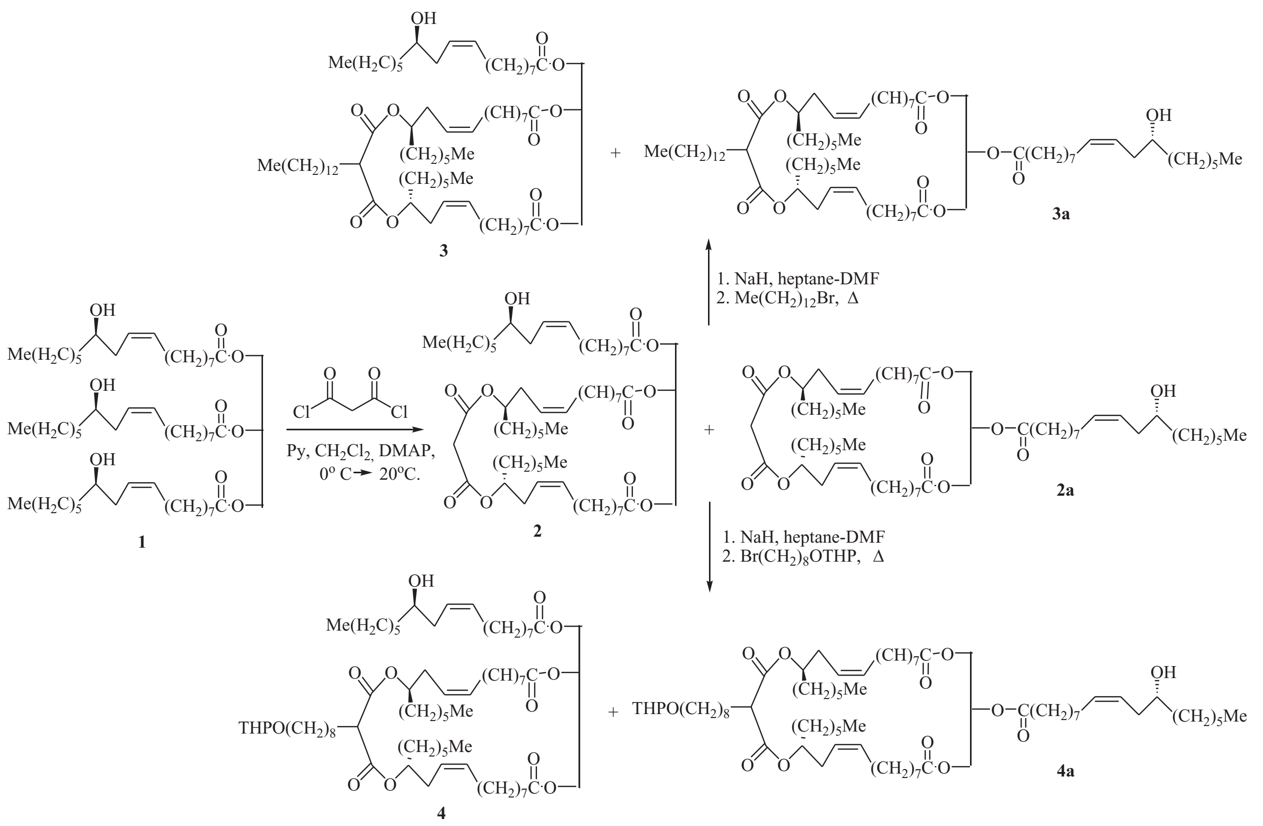
C-Alkylation reactions (general method). Macroheterocycles **2** and/or **2a** (4.0 g, 4.0 mmol) were added to the solution of NaH (4.0 mmol) in 4.0 mL of dry *n*-heptane and 4.0 mL of dry DMF with cooling to 0 °C in an inert atmosphere of argon. The reaction mixture was stirred before full dissolution of NaH (for ~3 hours) at room temperature, then 4.0 mmol of bromide (tridecyl- or 1-tetrahydropiranyloxyoct-8-yl bromides) were added at 0 °C. The reaction mixture was stirred for 11 hours at room temperature with TLC control after boiling for 12 hours. Saturated NH_4Cl solution (4 mL) was added to the reaction mixture with following extraction with heptane (4×30 mL), then the extracts were washed with a saturated NaCl solution (3×7 mL), dried with $MgSO_4$ and evaporated.

*13R,19R-Dihexyl-16-tridecyl-33-(2’-oxa-3’-oxo-14’R-hydroxyeicos-11’Z-en-1’-yl)-1,14,18,31-tetraoxa-2,15,17,30-tetraoxocyclotritricosa-10Z,21Z-diene (**3**) (and/or 13R,19R-dihexyl-16-tridecyl-33-(1’-oxa-2’-oxo-13’R-hydroxynonacos-10’Z-en-1’-yl)-1,14,18,31-tetraoxa-2,15,17,30-tetraoxocyclotetratricosa-10Z,21Z-diene (**3a**)).* Yield: 3.70 g (80 %). *m/z* $C_{73}H_{130}O_{11}$ (1183.8067) (ESI, Irelative, %): Scan (C+): 1202.10 (0.50) $[M+H_2O+H]^+$, 1184.21 (0.41) $[M+H]^+$; Scan (C-): 1182.11 (0.17) $[M-H]^-$, 884.60 (30.72) $[M-C_{18}H_{34}O_3-H]^-$. IR (KBr) ν_{max} cm^{-1}: 1733, 1740 (C=O), 3518 (OH). ^1H NMR ($CDCl_3$) δ_H ppm: 0.70 (12H, t, *J* = 6.4 Hz, H-20’, 2H-6’’, H-13’’’), 0.97–1.32 (74H, m, H-4÷H-8, H-24÷H-28, H-5’÷H-9’, H-16’÷H-19’, 2(H-2”÷H-5”), H-3’’’÷12’’’), 1.40–1.53 (8H, m, H-15’, 2H-1’’, H-2’’’), 1.87–1.95 (6H, m, H-9, H-23, H-10’), 2.03 (2H, m, H-1’’’), 2.10–2.21 (6H, m, H-12, H-13’, H-20), 2.17 (6H, t, *J* = 7.2 Hz, H-3, H-16, H-29, H-4’), 3.18 (1H, br.s, OH), 3.45–3.50 (1H, m, H-14’), 3.89 (1H, t, *J* = 6.2, H-16), 4.12–4.20 (4H, m, H-32, H-1’), 4.89–4.97 (2H, m, H-13, H-19), 5.08–5.20 (1H, m, H-33), 5.23–5.47 (6H, m, H-10, H-11, H-21, H-22, H-11’, H-12’). ^{13}C NMR ($CDCl_3$) δ_C ppm: 13.89 (q, C-20’, C-6”, C-13’’’), 22.37, 22.44, 22.48 (t, C-5’’, C-19’, C-12’’’), 24.05, 25.25, 24.61, 24.76 (t, C-2’’, 4, 5’, 7, 16’, 25, 28), 25.63, 25.67, 25.74, 26.89, 27.16 (t, C-5, C-6, C-9, C-23, C-26, C-27, C-10’) 28.33, 28.39, 28.46, 28.59, 28.72, 28.89, 28.94, 29.07, 29.17, 29.21, 29.27, 29.30, 29.34, 29.37, 29.46, 29.48, 29.51 (t, C-2’’’÷C-10’’’, C-3’’, C-6’÷C-9’, C-8, C-17’, C-24), 31.69, 31.69, 32.53, 32.65 (t, C-4’’, C-11’’’, C-12, C-13’, C-18’, C-20), 33.83 (t, C-3, C-29), 34.08 (t, C-4’) 35.15 (CH_2, C-1’’), 36.62 (t, C-15’), 42.53 (t, C-16), 61.84 (CH_2, C-1’, C-32), 68.73 (d, C-33), 71.17 (d, C-14’), 73.41 (d, C-13, C-19), 124.82 (d, C-11, C-21), 125.42 (d, C-12’), 132.22 (d, C-11’, C-10, C-22), 162.60 (s, C-15, C-17), 172.46, 172.85, (s, C-2, C-3’, C-30).

*13R,19R-Dihexyl-16-[8’’’-(tetrahydro-2H-piran-2’’’’-yloxy)octyl]-33-(2’-oxa-3’-oxo-14’R-hydroxyeicos-11’Z-en-1’-yl)-1,14,18,31-tetraoxa-2,15,17,30-tetraoxocyclotritricosa-10Z,21Z-dien (**4**) (and/or 13R,19R-dihexyl-16-[8’’’-(tetrahydro-2H-piran-2’’’’-yloxy)octyl]-33-(1’-oxa-2’-oxo-13’R-hydroxynonacos-10’Z-en-1’-yl)-1,14,18,31-tetraoxa-2,15,17,30-tetraoxocyclotetratricosa-10Z,21Z-diene (**4a**)).* Yield: 4.60 g (95 %). *m/z* $C_{73}H_{128}O_{13}$ (1213.7896) (ESI, Irelative, %): Scan (C+): 1232.18 (0.38) $[M+H_2O+H]^+$, 1214.73 (0.31) $[M+H]^+$; Scan (C-): 1212.41 (0.15) $[M-H]^-$, 914.81 (39.39) $[M-C_{18}H_{34}O_3-H]^-$. IR (KBr) ν_{max} cm^{-1}: 1733, 1740 (C=O), 3518 (OH). ^1H NMR ($CDCl_3$) δ_H ppm: 0.77 (9H, t, *J* = 6.5 Hz, H-20’, 2H-6’’), 0.97–1.32 (62H, m, H-4÷H-8, H-24÷H-28, H-5’÷H-9’, H-16’÷H-19’, 2(H-2”÷H-5”), H-3’’’÷6’’’), 1.39–1.70 (17H, m, H-15’, 2H-1’’, H-2’’’, 7’’’, 2’’’’-5’’’’), 1.85–1.93 (6H, m, H-9, H-23, H-10’), 2.01–2.20 (8H, m, H-1’’’, H-12, H-13’, H-20), 2.31 (6H, t, *J* = 7.1 Hz, H-3, H-16, H-29, H-4’), 3.20 (1H, br.s, OH), 3.31–3.50 (1H, m, H-14’), 3.75–3.87 (3H, m, H-8’’’, H-6’’’’), 3.89 (1H, t, *J* = 5.9 Hz, H-16), 3.99–4.10 (4H, m, H-32, H-1’), 4.57–4.98 (2H, m, H-13, H-19), 5.00–5.20 (1H, m, H-33), 5.21–5.49 (6H, m, H-10, H-11, H-21, H-22, H-11’, H-12’). ^{13}C NMR ($CDCl_3$) δ_C ppm: 13.94 (q, C-20’, C-6”), 19.49 (t, C-4’’’’), 22.52, 22.47 (t, C-5’’, C-19’), 24.28, 24.64, 24.80, 25.00, 25.35, 25.57, 25.71, 25.99, 26.24 (t, C-2’’, 4, 5’, 7, 16’, 25, 28, 9, 23, 17’, 4’’’’, 5’’’’, 10’), 26.83, 27.20 (t, C-5, C-6, C-26, C-27), 28.32, 28.46, 28.65, 28.94, 29.01, 29.07, 29.16, 29.23, 29.41, 29.53 (t, C-2’’’÷C-6’’’, C-3’’, C-6’÷C-9’, C-8, C-7’’’, C-24), 30.48, 30.60, 31.52, 31.71, 32.45, 32.62 (t, C-4’’, C-12, C-13’, C-18’, C-20, 3’’’’), 33.80, 33.90, 34.14 (t, C-3, C-29, 4’), 35.22 (t, C-1’’), 36.91 (t, C-15’), 43.04 (t, C-16), 62.06 (t, C-1’, C-32), 64.16 (t, C-6’’’’), 64.89 (t, C-8’’’’), 67.38 (d, C-33), 68.74 (d, C-14’), 71.20 (d, C-13, C-19), 98.61 (d, C-2’’’’), 124.86 (d, C-11, C-21), 125.38 (d, C-12’), 132.48 (d, C-11’, C-10, C-22), 162.71 (s, C-15, C-17), 172.97, 173.69, (s, C-2, C-3’, C-30).

Results and Discussion

Earlier, we have reported for the first time[4] on the one-stage synthesis of three macrocycles with four ester groups



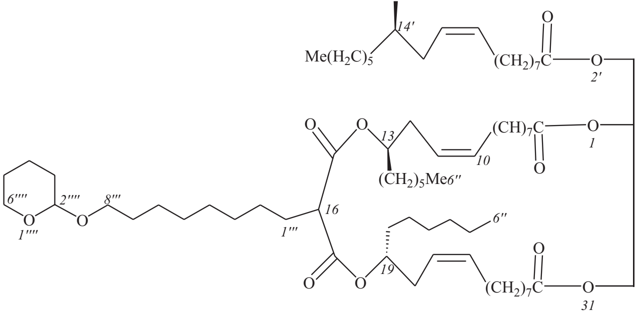
Scheme 1.

based on [1+1]-condensation of castor oil with dichloroanhydrides of succinic, glutaric and adipic acids. Continuing these studies, we have carried out the [1+1]-condensation of castor oil (**1**) with total malonic acid chloride at room temperature in absolute CH_2Cl_2 in the presence of pyridine and DMAP catalyst. As a result, macrocycles **2** and/or **2a** with a malonic fragment with 96 % yield were obtained. Subsequent *C*-alkylation reactions of the malonate spacer with tridecyl- or 1-tetrahydropiranyloxyoct-8-yl bromides in the presence of NaH in the *n*-heptane-DMF mixture resulted in formation of macrocycles **3**, **4** and/or **3a**, **4a** (Scheme 1).

The structures of all obtained macrocycles were determined by ^{1}H NMR and ^{13}C NMR spectroscopy and chromatography-mass spectrometry.

The absence of resonances at 8.0–10.0 ppm in the ^{1}H NMR spectra and at 178–180 ppm in the ^{13}C NMR spectra of the reaction products **2**,**2a** indicates that the obtained samples do not contain impurities of malonic acid, which could be formed by decomposition of the corresponding acid chloride and the adduct according to one of the carboxyl groups. The signals at 4.80–4.90 ppm in the ^{1}H NMR spectra of compounds **2** and/or **2a** correspond to –C(O)O–CH– protons, the integrated intensities of the resonances at 3.50-3.61 for hydroxyl protons being in agreement with formation of two ester fragments in macrocycles **2** and/or **2a**. The signals at 68.84 ppm of –CH–OH group, at 72.99 ppm of two –CH–OC(O)– groups and at 166.29 ppm of –CH–OC(O)– fragment in the ^{13}C NMR spectra, as well as a shift of the double-bond resonance under the influence of the formed esters (125.27 and 132.93 ppm) as compared with the double-bond resonances in castor oil (**1**) (125.20 and 132.43 ppm) are also indicative of this. All these spectral data, as well as mass spectral data confirm the formation of macrocycles **2** and/or **2a**.

The presence of additional resonances in the ^{1}H and ^{13}C NMR spectra of compounds **3**, **4** and/or **3a**, **4a,** resulting from the *C*-alkylation reaction of macrocycles **2** and/or **2a**, are observed. The integral intensity of proton signal at 4.05 ppm corresponds to two protons of –O–C(O)–CH_2–C(O)–O– fragment in the C-16 position of the initial compounds **2** and/or **2a**. In the case of the substitution reaction products **3**, **4** and/or **3a**, **4a** this resonance shifts at 3.89 ppm and its integral intensity corresponds to one proton of the –O–C(O)–CHR–C(O)–O– group. There are also some changes in the ^{13}C NMR spectrum, *viz.* the triplet



Scheme 2. 13*R*,19*R*-Dihexyl-16-[8’”-(tetrahydro-2*H*-piran-2””-yloxy)octyl]-33-(2’-oxa-3’-oxo-14’*R*-hydroxyeicos-11’*Z*-en-1’-yl)-1,14,18,31-tetraoxa-2,15,17,30-tetraoxocyclotritricosa-10*Z*,21*Z*-diene (**4**).

resonance at 49.29 ppm (C-16) turns to doublet at 42.53 ppm (for **3** and/or **3a**) or 43.04 ppm (for **4** and/or **4a**).

All these spectral data indicate the formation of the corresponding macrocycles (**2**, **2a**, **3**, **3a**, **4**, **4a**), which is further confirmed by mass spectrometry data. In the mass spectra of compounds **2**, **2a**, **3**, **3a**, **4**, **4a**, intense peaks of protonated MH^+ and deprotonated (M-H) ions, as well as their ionic associates with water molecules were registered, which can be considered as a proof of the existence of compounds with the corresponding molecular masses.

Conclusions

Thus, in this work, the [1+1]-condensation reaction of natural castor oil (triglyceride (*R*,*Z*)-(+)-12-hydroxy-9-octadecenoic acid) with acid chloride of malonic acid was carried out by one-step synthesis to obtain enantiomer of pure macroheterocycles with four ester groups and malonic fragment. The malonic fragment was further modified by C-alkylation reactions with tridecyl- or 1-tetrahydropyranyloxy-8-yl bromides.

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