

Interaction of 7-Oxoocetyl-7-oxooctanoate and bis(7-Oxoocetyl)hexanedioate with Phthalic Dihydrazide

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We have studied the interaction of 7-oxoocetyl-7-oxooctanoate and bis(7-oxoocetyl)hexanedioate, available from tetrahydropyran, with phthalic dihydrazide. It was found, that instead of expected macrolides containing hydrazide fragments, the corresponding macrocycles containing azine fragments are formed. Such compounds were obtained earlier via the interaction of substrates and hydrazine hydrate.

Keywords: Tetrahydropyran, α,ω -diketones, phthalic acid hydrazide, [1+1]-condensation, macrolides with azine fragment, synthesis.

Взаимодействие 7-оксооктил-7-оксооктаноата и бис(7-оксооктил)гександиоата с дигидразидом фталевой кислоты

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Изучено взаимодействие доступных из тетрагидропирана 7-оксооктил-7-оксооктаноата и бис(7-оксооктил)гександиоата с дигидразидом фталевой кислоты и установлено, что вместо ожидаемых макролидов с гидразидными фрагментами образуются соответствующие макроциклы с азинным фрагментом, ранее полученные при взаимодействии субстратов с гидразингидратом.

Ключевые слова: Тетрагидропиран, α,ω -дикетоны, дигидразид фталевой кислоты, [1+1]-конденсация, макролиды с азинным фрагментом, синтез.

We have already reported^[1-9] on the synthesis of a whole range of macroheterocycles with ester, azine and hydrazide fragments using key α,ω -diketones (**2**, **3**) available, in turn, from tetrahydropyran.^[2,10]

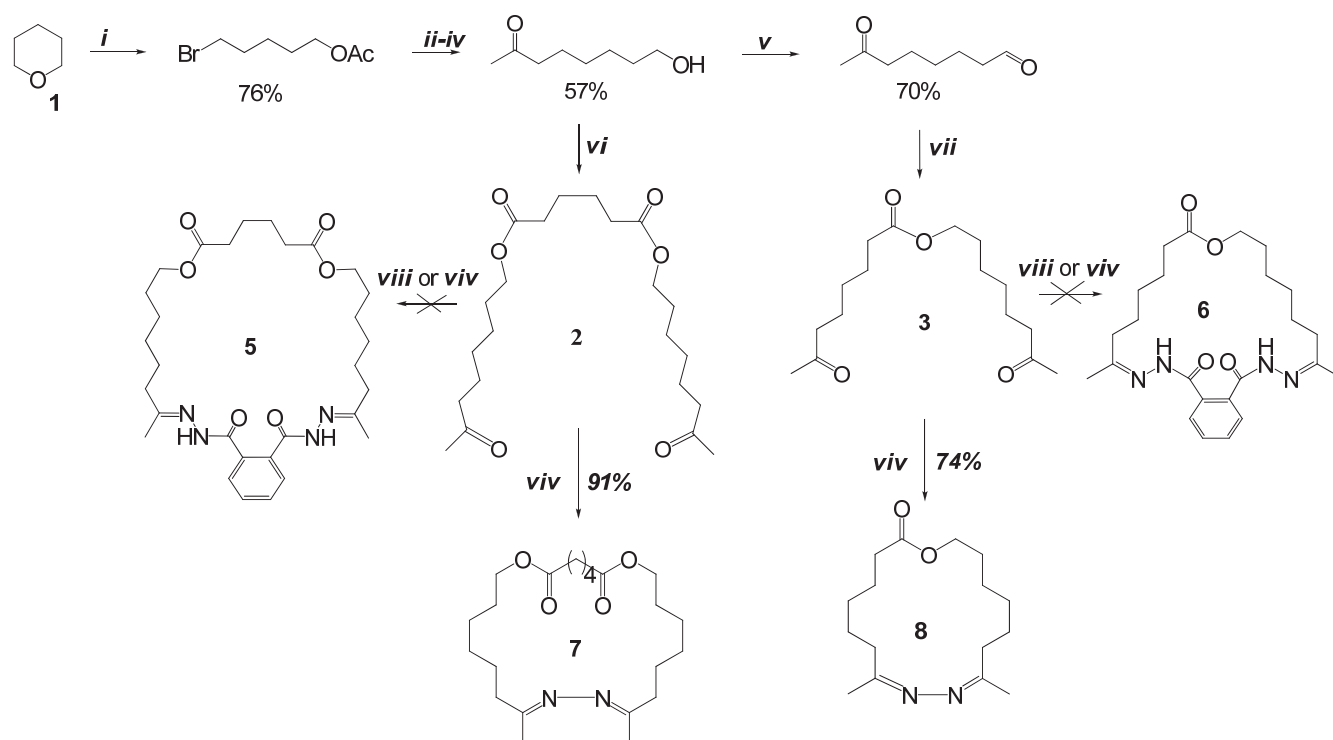
This report considers an unusual cyclization reaction of diketo diester (**2**) and diketo ester (**3**) under the influence of phthalic dihydrazide (**4**).

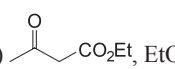
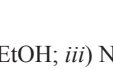
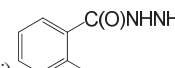
We have found that at room temperature the [1+1]-condensation reaction of α,ω -diketones **2** or **3** with dihydrazide **4** in dioxane under high-dilution conditions does not result, even with a low yield, in macrolides (**5** or **6**) containing phthalic dihydrazide fragments. The same situation is observed when using an equimolar mixture

of dioxane and water as a solvent; in this case, however, the corresponding azines (**7** or **8**) derived previously via [1+1]-condensation of the above-mentioned substrates (**2** and **3**) with hydrazine hydrate are formed with high yields.^[1,3,5,6]

It is apparent that in these reactions a lower reactivity of dihydrazide **4** is conditioned by participation of the conjugated aromatic fragment that causes a decrease in basicity of NH_2 -groups. In turn, the formation of macrolides (**7** or **8**) with azine fragments can be explained by the possibility of hydrazine to be generated in the breakdown of phthalic dihydrazide^[11-13] and its involvement into the [1+1]-condensation reaction with diketones (**2** and **3**).

Condensation Reaction of α,ω -Diketones with Phthalic Acid Dihydrazide



Reagent: *i*) AcBr/ZnCl₂; *ii*)  CO₂Et, EtONa/EtOH; *iii*) NaOH/H₂O; *iv*) H₂SO₄, H₂O; *v*) Na₂Cr₂O₇/H₂SO₄; *vi*) Cl  Cl, Py;
vii) Al(*i*-PrO)₃, hexane; *viii*)  (4), 1,4-dioxane; *viv*) (4), 1,4-dioxane-H₂O.

The structure of the obtained macrocycles (**7** and **8**) was determined by IR, ¹H, ¹³C NMR spectroscopy; the purity was analyzed by the HPLC method and reached not less than 96 %.

Experimental

Analyses of the compounds were performed on the equipment at the Chemistry Centre for Collective Use of the Institute of Organic Chemistry of the Ufa Scientific Centre of the Russian Academy of Sciences. Thin layer IR spectra were recorded on an IR Prestige-21 Shimadzu spectrometer (Fourier Transform Spectrophotometer – Shimadzu). NMR spectra were recorded on a BRUKER AM-300 spectrometer (operating frequency 300.13 MHz for ¹H and 75.47 MHz for ¹³C) in CDCl₃ and D₂O solutions with TMS internal standard. HPLC analyses were performed on a Shimadzu – LC-20AD liquid chromatograph with a 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 H₂O:CH₃CN (95:5) at a flow rate of 1 mL/min. The analytical wavelength was 215 nm. TLC monitoring used Sorbfil SiO₂ (Russia). Mass spectra of the synthesized compounds **7** and **8** were measured on a LCMS 2010 EV Shimadzu using atmospheric-pressure chemical ionization with electron energy 20 eV during the simultaneous recording of positive and negative ions. The liquid mobile phase (water and/or acetonitrile) has the carrier flow rate of 0.02 mL/min. Electron ionization mass spectra were recorded on a Finnigan MAT 95 XL chromatomass spectrometer with a data processing system at the ion source temperature 250 °C and ionization energy 70 eV. The sample input was performed using a HP-GC 6890 gas chromatograph. Accurate measurements of ion

mass numbers were made in the range between 1 and 3500 D at a resolution of 50,000.

15,18-Dimethyl-1,8-dioxa-16,17-diazacyclotetracos-15,17-diene-2,7-dione (7) and *8,11-dimethyl-1-oxa-9,10-diaza-8,10-cycloheptadecadiene-2-one (8)*. Under vigorous stirring, 0.194 g (1.0 mmol) of hydrazide **4** in 1.8 mL of H₂O was slowly added to 1.0 mmol of diketone (**2** or **3**) in 8.5 mL of dioxane. The mixture was stirred for 48 h (TLC monitoring), and then dioxane was evaporated under reduced pressure. The residue was dissolved in 20 mL of CH₂Cl₂, washed with water (3×5 mL), dried with Na₂SO₄ and evaporated. The resultant residue was sequentially added to 1 mL of dry CH₂Cl₂ and 10 mL of hexane under stirring and allowed to stand until the layers separate. Then the top layer was decanted. The residue was washed with 5 mL of hexane and evaporated *in vacuo*. The yields of **7** and **8** were 0.36 g (91 %) and 0.21 g (74 %), respectively. The IR, ¹H and ¹³C parameters and mass spectra of **7** and **8** were identical to those described previously.^[1,3]

In conclusion, we have found an unusual transformation in the [1+1]-condensation reaction of α,ω -diketones (bis(7'-oxooctyl)hexadioate or 7-oxooctanoic acid 7-oxooctyl ester) obtainable from tetrahydropyran with phthalic dihydrazide, that is the formation of macrolide azines instead of the expected dihydrazide derivatives.

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