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[1 + 1]-CONDENSATION OF 12-OXO-DERIVATIVES OF RICINOLEIC ACID ESTERS WITH HYDRAZINE HYDRATE ON THE ROUTE TO MACROCYCLES

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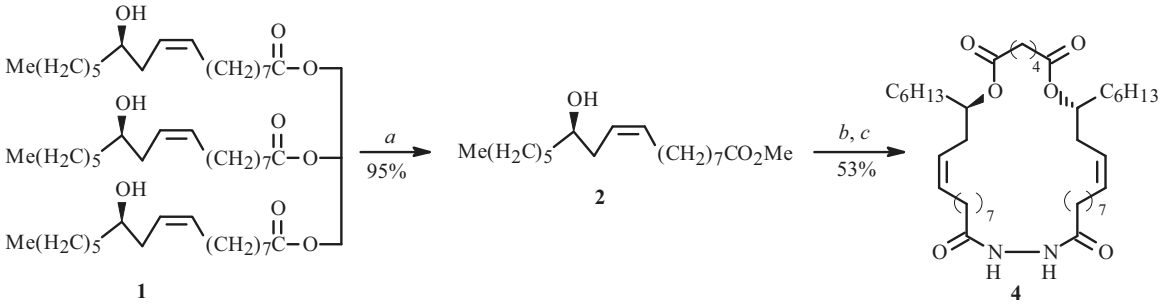
The reactivities of the keto analogs of methyl ricinolate and its triglyceride with hydrazine hydrate were studied. The ester was found to be inert, which made it possible to synthesize a macrocyclic azine with a side chain hydrazone moiety from a 12-oxo-derivative.

Keywords: methyl ricinoleate, castor oil, *O*,*N*-containing macroheterocycles, esters, hydrazone and azine moieties, synthesis.

Enantiomerically pure 34-membered macrolide **4** with a diacylhydrazine moiety was prepared quickly and efficiently by us earlier [1] from methyl ricinoleate (**2**), which is available via transesterification of castor oil (**1**) isolated from *Ricinus communis* seeds [2]. It consisted of sequential [2 + 1]-condensation of **2** with adipylchloride and [1 + 1]-condensation of the obtained *bis*[(9*Z*,12*R*)-1-methoxy-1-oxooctadec-9-en-12-yl]-1,4-hexanedicarboxylate (**3**) with hydrazine hydrate.



1 **2** **4**

a. MeOH, H^+; *b*. $ClOC(CH_2)_4COCl$, Py; *c*. $N_2H_4 \cdot H_2O$, 1,4-dioxane

In continuation of these studies, possible incorporation of 12-oxo-derivatives **5** and **6** of **2** and its triglyceride (castor oil, **1**) in the [1 + 1]-condensation with hydrazine hydrate was studied.

Corey oxidation of **2** to keto analog **5** followed by reaction with hydrazine hydrate in dioxane that occurred only at the ketones formed azine **7** and not macrocycle **8** with azine and diacylhydrazine moieties even if a large excess of hydrazine hydrate was used.

In a similar manner, the keto analog of castor oil **6** reacted to give macrocycle **9** and/or **10** in which one of the carbonyl groups was converted to a hydrazone whereas the other two were linked by an azine group. Isomers **9** and **10**, which differed in the size of the rings, could not be differentiated using NMR spectroscopy and mass spectrometry.

Disappearance in the IR spectra of bands at 1710 and 1715 cm^{-1} that were characteristic of the keto groups of starting **5** and **6** proved that hydrazine hydrate reacted with them. The appearance of bands at 1668 and 1663 cm^{-1} (C=N) proved that azine groups formed in **7** and **9** and/or **10**.

Retention in ^{13}C NMR spectra of ester resonances [173.95 ppm in **7** and 172.82 and 173.34 in **9** and/or **10**] and in PMR spectra of the resonance at 3.65 ppm corresponding to the OCH_3 group of **7** and two multiplets at 4.20–4.28 and 5.26–5.31 for CH_2 and CH groups of the glyceride moiety in **9** and/or **10** proved that the ester did not react with hydrazine hydrate. This indicated that the carboxylates were less reactive than the carbonyls.

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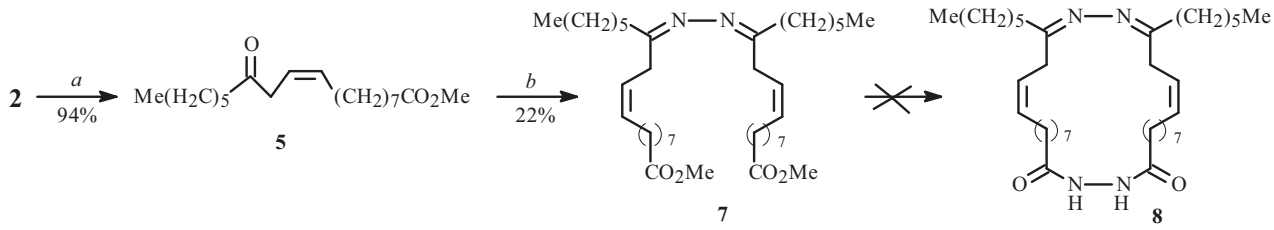
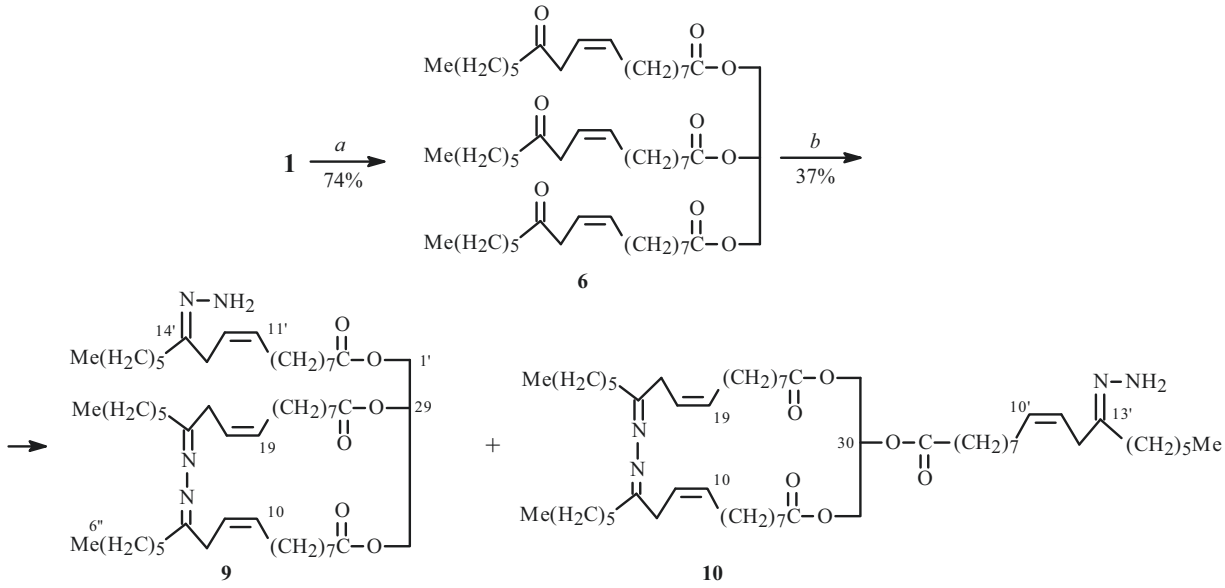


a. PCC, CH_2Cl_2; *b*. $NH_2NH_2 \cdot H_2O$, 1,4-dioxane



a. PCC, CH_2Cl_2; *b*. $NH_2NH_2 \cdot H_2O$, 1,4-dioxane

^{13}C NMR spectra were missing resonances for the carbonyls in **5** and **6** [208.81 and 209.01 ppm] and showed resonances at 154.00 that indicated azine groups had formed. Furthermore, PMR spectra of **9** and/or **10** contained a broad singlet at 5.56–5.61 ppm for an =N–NH_2 group.

All these results indicated that azine diester **7** and macrocyclic azine hydrazones **9** and/or **10** had formed. This was confirmed in mass spectra by the detection of the corresponding molecular masses, i.e., 616 $[M]^+$, 639 $[M + Na]^+$, and 655 $[M + K]^+$ for **7** and 936 $[M]^+$, 959 $[M + Na]^+$, and 975 $[M + K]^+$ for **9** and/or **10**.

Thus, the study of reactions of hydrazine hydrate with keto-derivatives of methyl ricinoleate and its triglyceride found that the esters were inert. This enabled a macrocyclic azine containing a side-chain hydrazone to be synthesized from the 12-oxo-derivative of castor oil.

EXPERIMENTAL

General comments were published before [3].

(*Z*)-Methyl 12-oxooctadec-9-enoate (5) was prepared from castor oil (**1**) by the literature method [4]. Yield 1.20 g (94%). IR spectrum (ν, cm^{-1}): 1710 (C=O), 1740 (CO_2), 3010 (CH=). ^1H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.89 (3H, t, J = 6.7, H-18), 1.21–1.38 (16H, m, H-4÷H-7, H-14÷H-17), 1.43–1.48 (2H, m, H-13), 1.57–1.61 (2H, m, H-3), 2.30 (2H, t, J = 7.0, H-2), 2.38–2.43 (2H, m, H-8), 3.13 (2H, d, J = 6.0, H-11), 3.65 (3H, s, OCH_3), 5.38–5.58 (2H, m, H-9, 10). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 13.96 (q, C-18), 22.54, 24.82, 25.63, 28.99, 29.0, 29.31, 29.48, 31.78 (all t, C-3÷7, C-14÷C-17), 27.27 (t, C-8), 33.93 (t, C-13), 35.28 (t, C-2), 36.76 (t, C-11), 51.25 (q, OCH_3), 120.89 (d, C-10), 133.19 (d, C-9), 174.09 (s, C-1), 208.81 (s, C-12). Mass spectrum (ESI): $CH_3CN–H_2O$, 95:5, (Scan+) *m/z*: 310 (M^+), 279 $(M – OCH_3)^+$.

Glyceryl tri-(12-oxo-9*Z*-octadecanoate) (6) was prepared from castor oil (**1**) by the literature method [5]. Yield 3.65 g (74%). IR spectrum (ν, cm^{-1}): 1715 (C=O), 1740 (CO_2), 3010 (CH=). ^{1}H NMR spectrum (300 MHz, $CDCl_3$, δ, ppm, J/Hz): 0.84 (9H, t, J = 6.7, 3(H-18), 1.20–1.50 (48H, m, 3(H-4÷H-7, H-14÷H-17)), 1.50–1.90 (6H, m, 3(H-3)), 1.90–2.00 (6H, m, 3(H-8)), 2.30 (6H, t, J = 6.5, 3(H-2)), 2.44 (6H, t, J = 7.0, 3(H-13)), 3.16 (6H, d, J = 6.0, 3(H-11)), 4.20–4.28 (4H, m, H-1′, 3′), 5.26–5.31 (1H, m, H-2′), 5.56–5.61 (6H, m, 3(H-9), 3(H-10)). ^{13}C NMR spectrum (75 MHz, $CDCl_3$, δ, ppm): 13.98 (q, 3(C-18)), 27.52 (t, 3(C-8)), 22.50, 23.84, 24.87, 28.93, 29.09, 29.31, 31.64 (all t, 3(C-3÷7, C-14÷C-17)), 34.02 ($\underline{C}H_2CO_2$C-1′, $\underline{C}H_2CO_2$C-3′), 34.18 (t, $\underline{C}H_2CO_2$C-2′), 41.71 (t, 3(C-11)), 42.36 (t, 3(C-13)), 62.14 (t, C-1′, 3′), 69.02 (d, C-2′), 121.13 (d, C-10), 133.49 (d, C-9), 172.76 and 173.14 (d, $\underline{C}O_2$C-2′; t, $\underline{C}O_2$C-1′, $\underline{C}O_2$C-3′), 209.01 (s, C-12). Mass spectrum (ESI, *m/z*): $CH_3CN–H_2O$, 95:5, (Scan+): 926 $[M]^+$, 949 $[M + Na]^+$.

General Method for Preparing Azines. Diketone **5** or **6** (1.0 mmol) in distilled dioxane (8.5 mL) was stirred vigorously, treated slowly dropwise with hydrazine hydrate (0.1 mL, 0.1 g, 2.0 mmol, 98%), and stirred for 24 h (TLC monitoring). The dioxane was evaporated at reduced pressure. The residue was dissolved in CH_2Cl_2 (10 mL), washed with H_2O (3 × 3 mL), dried over $MgSO_4$ and evaporated. The resulting residue was rinsed by decantation with hexane (100 mL) and dried *in vacuo*.

Dimethyl 12,15-Dihexyl-13,14-diazahexacosa-9,12,14,17-tetraenoate (7). Yield 0.45 g (22%). IR spectrum (ν, cm^{-1}): 1738 (C=O), 1668 (C=N). ^{1}H NMR spectrum (δ, ppm, J/Hz): 0.87 (3H, t, J = 6.7, H-18), 1.18–1.30 (16H, m, H-4÷H-7, H-14÷H-17), 1.55–1.61 (2H, m, H-3), 2.29 (2H, t, J = 7, H-2), 2.00–2.15 (2H, m, H-8), 2.90 (2H, t, J = 7.0, H-13), 3.05 (2H, d, J = 6.0, H-11), 3.69 (3H, s, OCH_3), 5.22–5.61 (2H, m, H-9, 10). ^{13}C NMR spectrum (δ, ppm): 13.77 (q, C-18), 22.29, 26.02, 26.31, 27.01, 28.83, 29.19, 31.27, 31.42, 35.99 (all t, C-3÷7, C-14÷C-17), 27.33 (t, C-8), 29.39 (t, C-11), 33.75 (t, C-2), 37.21 (t, C-13), 51.11 (q, OCH_3), 121.97 (d, C-10), 131.90 (d, C-9), 154.00 (s, C-12), 173.95 (s, C-1). Mass spectrum (ESI, *m/z*): $CH_3CN–H_2O$ 95:5, (Scan+): 616 $[M]^+$, 639 $[M + Na]^+$, 655 $[M + K]^+$.

13,16-Dihexyl-1,28-dioxa-14,15-diaza-29-(2′-oxa-14′-hydrazono-11′*Z*-eicosen-3′-on-1′-yl)-cyclotriaconta-10*Z*,13,15,18*Z*-tetraen-2,27-dione (9) and/or **13,16-dihexyl-1,28-dioxa-14,15-diaza-30-(1′-oxa-13′-hydrazono-10′*Z*-eicosen-2′-on-1′-yl)-cyclohentriaconta-10*Z*,13,15,18*Z*-tetraen-2,27-dione (10).** Yield 0.19 g (37%). IR spectrum (ν, cm^{-1}): 1739 (C=O), 1663 (C=N). ^{1}H NMR spectrum (δ, ppm, J/Hz): 0.81 (9H, t, J = 6.7, H-20′, 2(H-6′′)), 1.10–1.23 (48H, m, H-5÷H-8, H-21÷H-24, H-6′÷H-9′, H-16′÷H-19′, 2(H-2′′÷H-5′′)), 1.48–1.51 (6H, m, H-4, 25, 5′), 1.95–2.06 (6H, m, 3(H-8)), 2.23 (6H, t, J = 7, H-9, 20, 10′), 2.35 (6H, t, J = 7.0, H-15, 2(H-1′′)), 3.05 (6H, d, J = 6.0, H-12, 18, 13′), 4.15–4.25 (4H, m, H-30, 1′), 5.25–5.29 (1H, m, H-29), 5.51–5.57 (6H, m, H-10, 11, 18, 19, 11′, 12′), 5.58–6.01 (2H, br.s, NH_2). ^{13}C NMR spectrum (δ, ppm): 14.03 (q, C-20′, 2(C-6′′)), 27.52 (t, C-9, 20, 10′), 22.46, 23.84, 24.84, 28.02, 28.81, 29.09, 29.31, 31.52, 31.64 (all t, C-4÷C-8, C-21÷C-25, C-5′÷C-9′, C-16′÷C-19′, 2(C-2′′÷C-5′′), 34.00 (C-3, 4′), 34.07 (t, C-26), 41.71 (t, C-12, 18, 13′), 42.36 (t, C-15′, 2(C-1′′)), 63.69 and 65.08 (t, C-30, 1′; d, C-29), 120.13 (d, C-11, 18, 12′), 131.49 (d, C-10, 19, 11′), 153.03 (s, C-14′), 154.00 (s, C-13, 16), 172.76 (s, C-27), 173.14 (s, C-2, 3′). Mass spectrum (ESI, *m/z*): $CH_3CN–H_2O$ 95:5, (Scan+): 936 $[M]^+$, 959 $[M + Na]^+$, 975 $[M + K]^+$.

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