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SYNTHESIS OF A MULTIFUNCTIONAL PHEROMONE OF THE HONEYBEE *Apis mellifera* VIA CONDENSATION OF 7-OXOOCTANAL WITH MALONIC ACID

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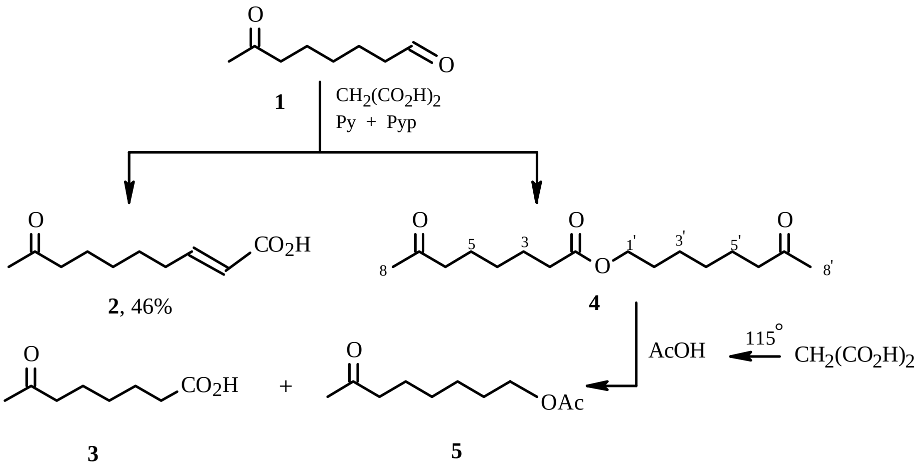
Condensation of 7-oxooctanal with malonic acid in a Doebner reaction produces 9-oxo-2E-decenoic acid (42% yield) and a comparable amount of products from Tishchenko disproportionation of the starting aldehyde (7-oxooctyl-7-oxooctanoate) and re-esterification by acetic acid (7-oxooct-1-ylacetate and 7-oxooctanoic acid).

Key words: pheromone, 9-oxo-2*E*-decenoic acid, 7-oxooctanal, 7-oxooctyl-7-oxooctanoate, 7-oxooct-1-ylacetate, 7-oxooctanoic acid, Doebner and Tishchenko reactions.

The most common method of introducing the α,β-unsaturated carboxylic acid in syntheses of 9-oxo-2*E*-decenoic acid, a multifunctional pheromone of the honeybee *Apis mellifera* L., is the Doebner condensation of 7-oxooctanal (**1**) with malonic acid that is accompanied by decarboxylation [1]. It has been noted [1, 2] that **1** is difficulty available and that the yields of the target pheromone **2** are low (32-47%). This is due to the instability of the ω-acetylalkanal **1** owing to the presence of the ketone. Attempts to protect this group by converting it to the ketal slightly increased the stability. However, the additional protection and deprotection steps increased the use of reagents and synthesis time without substantially affecting the yield of **2**.



During an investigation of the acidic products from the reaction of **1** and malonic acid under Doebner-condensation conditions (Py + Pyp), we detected 7-oxooctanoic acid (**3**) in addition to the target acid **2** (42% yield after recrystallization). The content of **3** in the mixture varied (GC monitoring) and its formation via oxidation of **1** could not be explained because the reaction was carried out under an inert atmosphere (Ar). Therefore, we analyzed the neutral reaction products.

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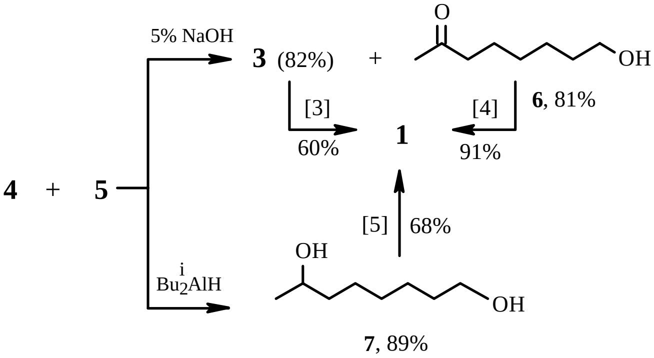
We found for the first time that a mixture of the 7-oxooctyl ester of 7-oxooctanoic acid (**4**) and 7-oxooct-1-ylacetate (**5**) that was approximately equal to the mass of the acid products was formed under the condensation conditions (Py + Pyp). These are products of Tishchenko disproportionation of **1** and subsequent re-esterfication, respectively. The acetic acid needed for **1** is formed via decarboxylation of the excess of malonic acid.

It should be noted that the ratio of esters **4** and **5** varies with time (from 2 to 4 h) under decarboxylation conditions (~115°C) in favor of the latter (from about 10 to 20%). As the re-esterification of **4** proceeds, the content of saturated ketoacid **3** in the acidic products (in the same ratio) increases. This leads to contamination of the target ketoacid **2**. Therefore, strict control of the decarboxylation and its conclusion after CO_2 evolution ceases (monitoring with a gas-bubble counter) are recommended.

Base hydrolysis of esters **4** and **5** gives **3** and ketoalcohol **6** in good yields. Hydride reduction produces diol **7**, which can be readily converted to starting **1** by known methods [3-5], which enables its conversion and the yield of pheromone to be increased (by 15-18%).



EXPERIMENTAL

IR spectra were recorded on a UR-20 instrument in thin layers. NMR spectra were taken on a Bruker AM-300 spectrometer (working frequency 300.13 MHz for ^{1}H and 75.47 MHz for ^{13}C) in $CDCl_3$ using the $CDCl_3$ signals as standards (in PMR, δ 7.27 ppm; in ^{13}C NMR, δ 77.00 ppm). Chromatographic analysis used a Chrom-5 instrument [column length 1.2 m, stationary phase silicone SE-30 (5%) on Chromaton N-AW-DMCS (0.16-0.20 mm), working temperature 50-300°C] with He carrier gas. Analytical data for the compounds agreed with those calculated.

9-Oxo-2*E*-decenoic Acid (2), 7-Oxooctanoic Acid (3), 7-Oxooctyl-7-oxooctanoate (4), and 7-Oxooctylacetate (5).

a. Malonic acid (10.44 g, 100 mmole) and **1** (11.00 g, 77.5 mmole, prepared as before [4]) were successively dissolved in dry pyridine (51 mL) and treated with piperidine (2.5 mL). The reaction mixture was stored (Ar; 20°C, 48 h; 60°C, 2 h; 115°C, 2 h), cooled, diluted with Et_2O (300 mL), successively washed with HCl (10%, until the pH was 2) and saturated NaCl solution (until the pH was 7), and treated with saturated $NaHCO_3$ solution (until the pH was 8). The organic layer was separated, dried over Na_2SO_4, and evaporated. A part (1 g) of the solid (5.2 g, **4**/**5** mixture, ~9:1 according to GC) obtained was chromatographed (SiO_2, hexane:Et_2O, 7:3).

The aqueous layer was acidified with HCl (until the pH was 2) and extracted with Et_2O (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The solid (7.2 g, **2**/**3** mixture, ~9:1 according to GC) was recrystallized from petroleum ether:Et_2O (1:1) to give **2** (5.53 g, 42%), the IR and PMR spectra of which are identical to those in the literature [6, 7].

b. Malonic acid (10.44 g, 100 mmole) and **1** (11.00 g, 77.5 mmole) were dissolved in dry pyridine (51 mL) and treated with piperidine (2.5 mL). The reaction mixture was stored (Ar; 20°C, 48 h; 60°C, 2 h; 115°C, 4 h) and worked up as described in **a** to give the neutral reaction products (4.7 g, **4**/**5** mixture, ~4:1 according to GC).

The aqueous layer was acidified with HCl (until the pH was 2) and extracted with Et_2O (3×100 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The solid (7.7 g, **2**/**3** mixture, ~4:1 according to GC) was recrystallized from petroleum ether:Et_2O (1:1) to give **2** (4.35 g, 33%), the IR and PMR spectra of which are identical to those in the literature [6, 7].

7-Oxooctyl-7-oxooctanoate (4), R_f 0.18 (SiO_2, petroleum ether:Et_2O, 7:3). PMR spectrum (δ, ppm, J/Hz): 1.30 (10H, m, H-2′—H-5′, H-3), 1.54 (4H, H-4, H-5), 2.09 (6H, s, H-8, H-8′), 2.24 (2H, t, J = 7.4, H-2), 2.39 (4H, t, J = 6.6, H-6, H-6′), 4.00 (2H, t, J = 6.6, H-1′). ^{13}C NMR spectrum: 23.25 (t, C-5′), 23.51 (t, C-5), 24.58 (t, C-3), 25.62 (t, C-3′), 28.33 (t, C-2′), 28.47 (t, C-4), 28.82 (t, C-4′), 29.77 (q, C-8, C-8′), 33.96 (t, C-2), 43.30 (t, C-6), 43.46 (t, C-6′), 64.15 (t, C-1′), 173.31 (s, C-1), 208.86 (s, C-7′), 208.99 (s, C-7).

7-Oxooctylacetate (5), R_f 0.33 (SiO_2, petroleum ether:Et_2O, 7:3). PMR spectrum (δ, ppm, J/Hz): 1.22 (4H, m, H-3, H-4), 1.51 (4H, m, H-2, H-5), 1.93 (3H, s, CH_3CO_2), 2.02 (3H, s, H-8), 2.33 (2H, t, J = 7.6, H-6), 3.93 (2H, t, J = 6.6, H-1). ^{13}C NMR spectrum: 19.55 (q, CH_3CO_2), 22.46 (t, C-5), 24.66 (t, C-3), 27.40 (t, C-2), 27.66 (t, C-4), 28.47 (q, C-8), 42.22 (t, C-6), 63.05 (t, C-1), 169.40 (s, CO_2), 206.83 (s, C-7).

7-Oxooctanoic Acid (3) and 8-Hydroxyoctan-2-one (6). The mixture of **4**/**5** (3.00 g, ~9:1 according to GC) and NaOH (0.55 g, 13.8 mmole) was dissolved in H_2O (11 mL), stored (20°C, 24 h; 60°C, 6 h), cooled, and extracted with Et_2O (3×50 mL). The combined extracts were dried over Na_2SO_4 and evaporated to give **6** (1.29 g, 81%), the IR and PMR spectra of which were identical to those in the literature [6].

The aqueous layer was acidified with conc. HCl, extracted with Et_2O (3×50 mL), dried over $MgSO_4$, and evaporated to give **5** (1.23 g, 82%), the IR and PMR spectra of which were identical to those in the literature [7].

1,7-Octandiol (7). The mixture of **4**/**5** (3.50 g, ~9:1 according to GC) in absolute Et_2O (129 mL) was treated dropwise under Ar at 0°C with DIBAH (22 mL, 73%) in toluene, stored for 2 h at the same temperature, and treated with H_2O (20 mL). The solid was filtered off and washed on the filter with Et_2O (100 mL). The filtrate was evaporated to give **7** (3.14 g, 90%), the IR and PMR spectra of which were identical to those in the literature [5].

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