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INSECT PHEROMONES AND THEIR ANALOGS.

XV. THE SYNTHESIS OF 9-OXODEC-2E-ENOIC ACID — A PHEROMONE OF THE HONEYBEE *Apis melliferana*

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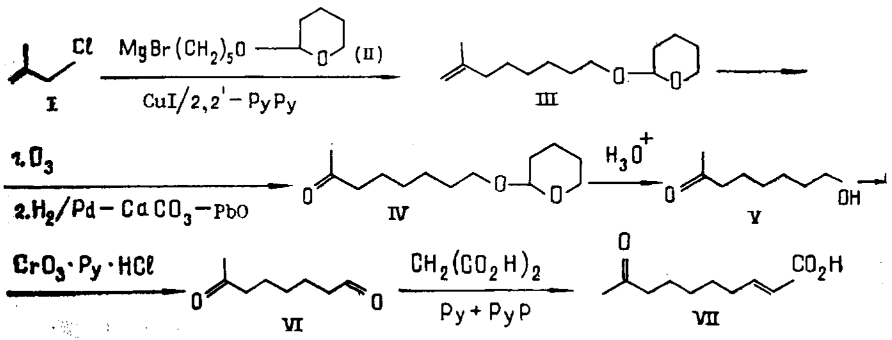
A new effective route to the synthesis of 7-oxooctanal has been found which is based on the ozonolysis of the tetrahydropyran-2-yl ether of 7-methyloct-7-en-1-ol — the product of the coupling of the readily available methallyl chloride and the Grignard reagent from the corresponding ether of 5-bromopentan-1-ol. From the 7-oxooctanal has been obtained 9-oxodec-2E-enoic acid — a pheromone of the honeybee *Apis melliferana*.

9-Oxodec-2E-enoic acid fulfills important functions in the vital activity of the honeybee *Apis melliferana* [1, 2]. A number of methods of synthesizing this compound are known [1, 3]. The introduction of the keto group has been effected by the $PdCl_2$-catalyzed oxidation of a vinyl group [1, 4], by the cleavage of 1-methylcyclopentanone or of thiophene derivatives [1], and by the action of methylmagnesium iodide on 7-hydroxyheptanal followed by oxidation with pyridinium chlorochromate [5, 6].



We have found a new route to the synthesis of the key synthon — 7-oxooctanal (VI), starting from the readily available methallyl chloride (I). The coupling of the latter with 5-(tetrahydropyran-2-yloxy)pentylmagnesium bromide (II) gives a high yield of the tetrahydropyran-2-yl (THPL) ether of 7-methyloct-7-en-ol (III), the ozonolysis of which leads to the 2-THPL ether (VIII) of 8-hydroxyoctan-2-one (V). Hydrolysis of the ether (IV) followed by oxidation of the hydroxy ketone (V) gives the desired keto aldehyde (VI) with an overall yield of 53% calculated on the bromo alcohol derivative (I). Condensation of the keto aldehyde (VI) with malonic acid under standard conditions [1, 4-6] leads to 9-oxide-2E-enoic acid (VII).

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EXPERIMENTAL

The PMR spectrum of compound (IV) was obtained on a Tesla BS-567 (100 MHz) instrument and the spectra of other compounds on a Tesla BS-467 (60 MHz) instrument using $CDCl_3$ as the solvent. The ^{13}C NMR spectrum was recorded on a JEOL FX-90Q instrument in regimes with broad-band and partial suppression of proton effects, again with $CDCl_3$ as solvent. The chemical shifts are given in the δ scale relative to the signal of TMS (internal standard). The IR spectra of the substances were recorded on a UR-20 spectrometer in a thin layer or in Nujol. GLC was performed on a Chrom-4 instrument with the stationary phase SE-30 (15%) on Chromaton N-AW-DMCS (0.16-0.20 mm) at a working temperature of 50-30°C with helium as the carrier gas.

7-Methyl-1-(tetrahydropyran-2-yloxy)oct-7-ene (III). A suspension of 2.4 g (12.6 mmole) of CuI in 50 ml of absolute THF was treated with 1.97 g (12.6 mmole) of 2,2'-bipyridyl and the mixture was stirred (under argon) at 20°C for 0.5 h; it was then cooled to 2°C and a solution of 5.5 g (60.7 mmole) of the chloride (I) in 10 ml of absolute THF was added and stirring was continued for another 10 min. Then the Grignard reagent obtained from 0.75 g (31.2 mg-atom) of magnesium and 7.65 g (30.5 mmole) of 5-bromo-1-(tetrahydropyran-2-yloxy) pentane (II) in 35 ml of absolute THF was added and the reaction mixture was stirred at 2°C for 2 h and then at 20°C for 15 h. It was then treated with 50 ml of saturated NaCl and was stirred at 10°C for 1 h, after which 0.5 liter of diethyl ether was added and the organic layer was separated off, washed with saturated NaCl, dried with Na_2SO_4, and evaporated. The residue was chromatographed (SiO_2, n-hexane–diethylether (15:1)). This gave 5.1 g (74%) of the THPL ether (III), n_D^{22} 1.4520. IR spectrum (ν, cm^{-1}): 890 s, 1040 s, 1085 s, 1125 s, 1143 s, 1655 m, 3080 w. PMR spectrum (δ, ppm): m 1.2–1.6 (14H, CH_2), s 1.7 (3H, $CH_3C{=}C$), m 2.0 (2H, $CH_2C{=}C$), t 3.56 (2H, CH_2O, J = 6.5 Hz), t, 3.76 (2H, CH_2O, J = 6.5 Hz), s 4.57 (2H, $CH_2{=}C$), t 4.67 (1H, OCHO, J = 1 Hz).

1-(Tetrahydropyran-2-yloxy)octan-7-one (IV). A mixture of ozone and oxygen (productivity of the ozonizer 45 mole of O_3/h) was passed at the rate of 30 liters/g through a solution of 3.0 g (13.3 mmole) of compound (III) in 50 ml of redistilled methanol at 0°C until 0.72 g (50 mmole) of ozone had been absorbed. The reaction mixture was purged with argon and then with hydrogen, and 0.05 g of Lidlar catalyst was added and the mixture was stirred at room temperature in an atmosphere of hydrogen until a test for peroxide compounds with an aqueous solution of potassium iodide had become negative (20-25 h). Then the catalyst was filtered off and was washed with 100 ml of diethyl ether. The filtrate was evaporated under reduced pressure. This gave 2.8 g (92%) of compound (IV), n_D^{20} 1.4450. IR spectrum (ν, cm^{-1}): 1030 s, 1075 s, 1120 s, 1130 s, 1160 m, 1705 s. PMR spectrum (δ, ppm): m 1.4-1.9 (14 H, CH_2), s 2.13 (3H, CH_3CO), t 2.49 (2H, CH_2CO, J = 6 Hz), t 3.5 (2H, CH_2O, J = 7 Hz), t 3.66 (2H, CH_2O, J = 7 Hz), t 4.61 (1H, OCHO, J = 1 Hz).

1-Hydroxyoctan-7-one (V). A solution of 2.6 g (11.4 mmole) of compound (IV) in 50 ml of methanol and 15 ml of water was treated with 0.3 g of p-TsOH, the mixture was stirred at room temperature for 20 h, the methanol was evaporated off under reduced pressure, and the residue was dissolved in 400 ml of diethyl ether, which was washed with 50 ml of saturated $NaHCO_3$ and then with 50 ml of saturated NaCl, dried with Na_2SO_4 and evaporated. This gave 1.4 g (85%) of the hydroxy ketone (V), n_D^{22} 1.4485 [7]. The IR and PMR spectra of compounds (V) were identical with those described in the literature [4, 7].

7-Oxooctanal (VI). With stirring, a solution of 0.9 g (6.2 mmole) of the hydroxyketone (V) in 15 ml of CH_2Cl_2 was added to a suspension of 2.0 g of pyridinium chlorochromate in 25 ml of redistilled CH_2Cl_2 (20°C, Ar). The reaction mixture was stirred at room temperature for 2 h and was then diluted with 200 ml of diethyl ether and was filtered with suction through a layer of SiO_2, and the residue on the filter was washed with 200 ml of diethyl ether. The solution was dried with $MgSO_4$ and evaporated. This gave 0.81 g (91%) of the keto aldehyde (VI), n_D^{22} 1.4403 [7]. The IR and PMR spectra of compound (VI) were identical with the spectra described in the literature [4, 7].

9-Oxodec-2-enoic Acid (VII). A solution of 0.76 g (5.35 mmole) of the keto aldehyde (VI), 0.72 g (6.9 mmole) of malonic acid, 0.17 ml of piperidine, and 3.5 ml of pyridine was kept at 22°C for 17 h and at 30°C for 6 h and was then heated at 120°C for 1.5 h, after which 250 ml of diethyl ether was added. Then it was washed with 3 ml of 15% HCl followed by 450 ml of saturated NaCl. The organic layer was treated with 100 ml of saturated $NaHCO_3$ (to pH 8-9), and the aqueous layer was separated off, acidified with concentrated HCl to pH ∿ 2) and reextracted with diethyl ether (3 × 150 ml) and the extract was dried with Na_2SO_4 and evaporated. This gave 0.45 g (46%) of the keto acid (VII), mp 52-54°C (diethyl ether–petroleum ether (2:1)) [7]. The IR and PMR spectra of compound (VII) were identical with the spectra described in the literature [4, 7]. ^{13}C NMR spectrum (ppm): t 23.43 (C^7), t 27.68 (C^6), t 28.59 (C^5), q 29.83 (C^{10}), t 32.05 (C^4), t 43.47 (C^8), d 120.83 (C^3), d 151.84 (C^2), s 171.74 (C^1), s 209.21 (C^9).

SUMMARY

A new effective route to the synthesis of 7-oxooctanal has been found which is based on the ozonolysis of 7-methyloct-7-en-1-ol — the product of the coupling of the readily available methallyl chloride and with the Grignard reagent from a derivative of 5-bromopentan-1-ol. From the 7-oxooctanol has been obtained 9-oxodec-2E-enoic acid — a pheromone of the honeybee Apis melliferana.

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