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AN IMPROVED AND SIMPLE SYNTHESIS OF METHYL OR ETHYL 7-OXOHEPTANOATE AND 7-ACETOXYHEPTANAL.

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Abstract: *Reaction of cycloheptanone with potassium persulfate, in ethanol or methanol, gave ethyl or methyl 7-hydroxyheptanoate which, by oxidation with PCC, were converted into ethyl or methyl 7-oxoheptanoate in good yields. Protection of aldehyde group of methyl 7-oxoheptanoate, followed by one-step conversion of carboxylic ester to the acetate gave, after regeneration of aldehyde group, 7-acetoxyheptanal.*

Methyl or ethyl 7-oxoheptanoate **3a,b** and 7-acetoxyheptanal **6** are uncommon aldehydes of special value in the synthesis of natural products.

Ethyl 7-oxoheptanoate **3b** has been used in the synthesis of (7Z,11E)- and (7Z,11Z)-7,11-hexadecadien-1-yl acetate[1], the pink bollworm moth pheromone, *Pectinophora gossypiella*, a very destructive pest of cotton in many areas of the world.

Methyl 7-oxoheptanoate **3a** has been utilized to prepare 2-(6-methoxycarbonylhexyl)-cyclopenten-2-en-1-one[2], a key intermediate for the synthesis of prostanoids[3], and to prepare

(7E,9Z)-7,9-dodecadien-1-yl acetate[4], the sex pheromone of *Lobesia botrana* female, an important pest of vineyards in southern Europe.

7-Acetoxyheptanal **6** was used to synthesize (7Z,11Z)- and (7Z,11E)-7,11-hexadecadien-1-yl acetate[5]; to (Z)-7-tetradecen-1-yl acetate[6], the pheromone of *Amathes c-nigrum* ; to (Z)-7-dodecen-1-yl acetate and (Z)-7-tetradecen-1-yl acetate[7].

Ethyl 7-oxoheptanoate **3b** has been previously obtained by oxidation of 1-ethoxy cycloheptene[1], but the yield was not reported.

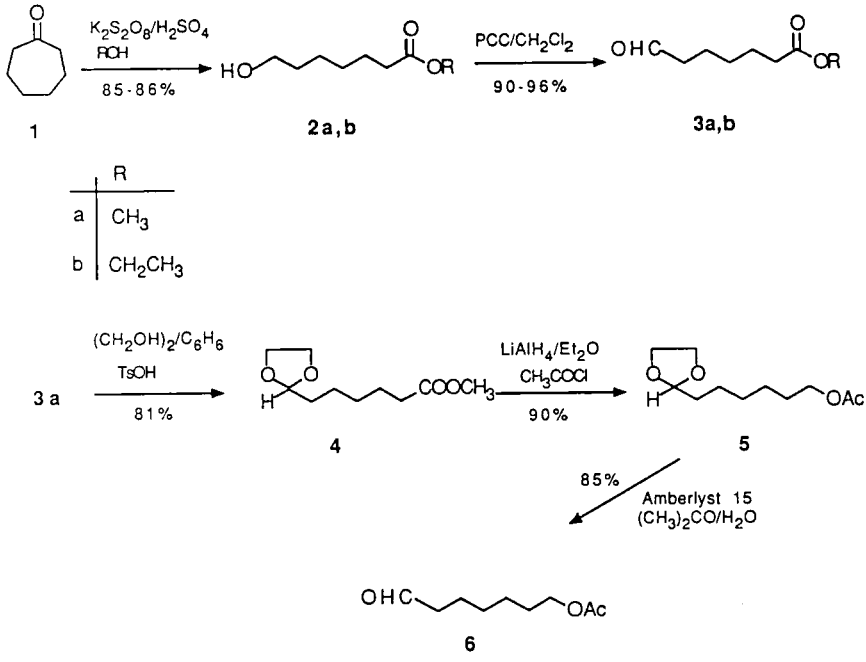
Methyl 7-oxoheptanoate **3a** was prepared from cycloheptanone[8], from 1-methoxy cycloheptene[9], from suberic acid[10], from methyl 7-iodoheptanoate[11], from 6-bromohexanoic acid or from ϵ-caprolactone[12] and from α-nitrocycloheptanone[13].

7-Acetoxyheptanal **6** was synthetisized from aleuritic acid[5], from suberic acid[4], from 4-iodobutyl acetate and 2-(2-bromoethyl)-1,3-dioxolane[14].

As part of a program aimed at the synthesis of pheromones we needed a convenient method to obtain the title compounds, so here we wish to report an advantageous, high yield and inexpensive synthesis of the compounds **3a,b** and **6**, even in a large scale, starting from cycloheptanone **1** as unique precursor. Although the aldehyde **3a** has been, previously, prepared from cycloheptanone[8], the yield obtained was not good (42% from the starting material), so here we describe an improved synthesis of **3a** and a new one for **3b** and **6**.

Reaction of cycloheptanone **1** with three equiv. of potassium persulfate, in methanol or ethanol[15,16] in the presence of sulfuric acid, gave methyl **2a** or ethyl **2b** 7-hydroxyheptanoate in 86% and 85% yields. Oxidation of alcohol with PCC afforded methyl **3a** or ethyl **3b** 7-oxoheptanoate in 83% and 77% overall yields from **1**.

The aldehyde **3a** was then converted into its acetal **4** followed up the transformation of the ester group to acetate **5**, in one step[17], using



lithium aluminum hydride and acetyl chloride. Subsequent deprotection of compound **5** in acetone-water, with Amberlyst-15 furnished[18] the free 7-acetoxyheptanal **6** in 51% overall yield from **1**.

In summary, the cheap and easy procedure, the simple purifications required, the mild reaction conditions, the good yields and high purity of the products, make the present synthesis a convenient, alternative synthetic method to prepare the title compounds, also in a large scale.

Experimental.

IR spectra were obtained using a Perkin-Elmer 257 spectrophotometer. ^{1}H-NMR spectra were recorded, in $CDCl_3$ as solvent, using a Varian EM 390 instrument. Mass spectra were obtained using a Hewlett-Packard GC/MS 5988A. Microanalyses were obtained using a Hewlett-Packard

Analyzer Model 185. All the reactions were monitored by GC analyses using a Carlo Erba Fractovap 4160 instrument, with an OV1 capillary column. Boiling points are uncorrected. Cycloheptanone was purchased from Aldrich Chemical Co.

7-Hydroxyheptanoate (2):

A mixture of 96% sulfuric acid (70ml, 1.26 mol), water (24ml) and ethyl or methyl alcohol (100ml) is cooled at 15°C. Potassium persulfate (72.16g, 0.266mol) is added gradually with stirring at 10-15°C. A solution of cycloheptanone (9.96g, 0.089mol) in ethyl or methyl alcohol (30ml) is added dropwise at 15°C and the mixture is allowed to react at r.t. for 5 h, then the mixture is diluted with water (700 ml) and extracted with diethyl ether (3x200ml). After drying ($MgSO_4$), evaporation and distillation the pure **2** is obtained.

Methyl 7-hydroxyheptanoate (**2a**): 12.24g (86%); $bp_{0.1}$ 91-94°C (Lit.[12] $bp_{1.5}$ 121-123°C). IR(film): ν = 3400(OH), 1725(CO) cm^{-1}. ^{1}H-NMR($CDCl_3$): δ=1.2-1.4(m,4H), 1.5-1.65(m,4H), 2.27(t,2H, J=7.5Hz), 2.5(s,1H), 3.55(t,2H, J=6.4Hz), 3.62(s,3H). MS: *m/z* = 130, 87, 74, 55, 41, 31.

Ethyl 7-hydroxyheptanoate (**2b**): 13.16g (85%); $bp_{0.1}$ 110-112°C (Lit.[16] bp_{14} 114°C). IR(film): ν = 3400(OH), 1725(CO) cm^{-1}. ^{1}H-NMR($CDCl_3$): δ= 1.2(t,3H, J=7.5Hz), 1.05-2.05(m,8H), 2.3(t, 2H, J=6.4Hz), 2.65(s,1H), 3.5(t,2H, J=6.04Hz); 4.1(q,2H, J=7.5Hz). MS: *m/z* = 144, 101, 74, 55, 41, 31.

7-Oxoheptanoate (3):

To a stirred suspension of pyridinium chlorochromate (PCC) (32.8g, 0.152 mol), molecular sieve (3A, 20g), in dichloromethane (150 ml), **2** (0.0624mol) is added dropwise. After stirring for 1 h at r.t. and

addition of diethyl ether (300ml), the solution is passed through a short pad of Florisil (30-60 mesh) and the solvent is removed under reduced pressure. Distillation of the oily residue gives the pure **3**.

Methyl 7-Oxoheptanoate (**3a**): 9.38g (96%); $bp_{0.2}$ 70°C (Lit.[8] $bp_{0.1}$62°C). IR(film): ν = 1730(CO) cm^{-1}. ^1H-NMR($CDCl_3$): 1.2-1.4(m,2H), 1.55-1.7(m,4H), 2.25-2.4(m,4H), 3.62(s,3H), 9.7(t,1H, J=2Hz). MS: *m/z* = 130, 115, 87, 74, 55, 43, 29.

Ethyl 7-Oxoheptanoate (**3b**): 9.6g (90%); $bp_{0.2}$ 88-91°C.

IR(film): ν = 1725 (CO) cm^{-1}.

^1H-NMR($CDCl_3$): δ= 1.2(t,3H, J=7.0Hz), 1.05-2.05(m,8H), 2.3(t,2H, J=6.0Hz), 4.1(q,2H, J=7.0Hz), 9.7(t,1H, J=2Hz).

MS: *m/z* = 124, 101, 74, 55, 41, 29.

Methyl 6-(1,3-dioxolan-2-yl)hexanoate (4):

A mixture of methyl-7-oxoheptanoate **3a** (8g, 0.0504 mol) and ethylene glycol (37.44g, 0.604 mol) in benzene (600ml) containing toluene p-sulfonic acid monohydrate (2g, 0.01mol) is refluxed for 4 h (the starting material is consumed GC), water being segregated by Dean and Stark separator. The mixture is then poured into 5% aqueous sodium hydrogen carbonate and the benzene layer, washed and dried ($MgSO_4$), affords, on evaporation, **4** as an oil, further purified by distillation: 8.26g (81%); $bp_{0.1}$ 90-92°C. IR(film): ν = 1725(CO) cm^{-1}. ^1H-NMR($CDCl_3$): δ = 1.25-1.45(m,4H), 1.55-1.65(m,4H), 2.27(t,2H, J=7.5Hz), 3.60(s,3H), 3.75-3.80(m,2H), 3.90-3.95(m,2H), 4.80(t,1H, J= 6.4Hz). MS: *m/z* = 201(M^+-1), 187, 111, 73, 59, 41, 29.

2-(6-Acetoxyhexyl)-1,3-dioxolane (5):

To a well stirred suspension of $LiAlH_4$ (0.9g, 0.0236mol) in ether (85ml), a solution of **4** (8g, 0.0394mol) is added dropwise with stirring, keeping a moderate reflux. The resulting mixture is heated at reflux for 4 h and then cooled at r.t.. Acetyl chloride (7.3g, 0.0936mol)

is added dropwise to the reaction mixture, which is heated at reflux for 5 h. The resulting mixture is cooled to 0°C and then quenched with 10% aqueous tartaric acid solution, to dissolve the precipitate formed during the decomposition. After extraction with ether (3x50ml), the organic layer is neutralized by washing with 5% aqueous sodium hydrogen carbonate (50ml) and brine (30ml). The solution is dried ($MgSO_4$), concentrated in vacuo, and the residue is purified by distillation to obtain the pure **5**: 7.38g (90%), $bp_{0.3}$ 81-83°C. IR(film): ν = 1735(CO) cm^{-1}. ^{1}H-NMR($CDCl_3$): δ = 1.25-1.45(m,4H), 1.55-1.65(m,4H), 2.00(s,3H), 3.7-4.0(m,8H), 4.6(t,1H, J=6.5Hz). MS: *m/z* = 216(M^+), 201, 171, 73, 55, 45, 29.

7-Acetoxyheptanal (6):

To a solution of **5** (6.0g, 0.0276mol) in acetone (110ml) containing water (3ml) is added Amberlyst 15 (1.05g) and the mixture is stirred for 24 h, then the resin is filtered and the filtrate is evaporated to give **6** as an oil which is further purified by distillation: 3.7g(85%), $bp_{0.3}$ 81-86°C (Lit.[14] $bp_{0.7}$93-98°C). IR(film): ν = 1735(CO) cm^{-1}. ^{1}H-NMR($CDCl_3$): δ = 1.3-1.4(m,4H), 1.55-1.65(m,4H), 2.05(s,3H), 2.38-2.45(m,2H), 4.00(t,2H, J=6.48Hz), 8.75(t,1H, J=2Hz).

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