[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Acetoacetic Ester Condensation. V. The Condensation of Higher Esters

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In an earlier paper[1] it was pointed out that ethyl α-propionylpropionate and ethyl α-butyrylbutyrate could be prepared in excellent yields through an acetoacetic ester condensation of ethyl propionate and ethyl butyrate. The essential feature of the procedure was the prevention of the reversal of the condensation, $2RCH_2COOC_2H_5 + NaOC_2H_5 \rightleftharpoons RCH_2C(ONa)=C(R)COOC_2H_5 + 2C_2H_5OH$ by removal of the alcohol as it was formed in the reaction mixture. This was accomplished by periodic distillations of portions of the ester, which had been used in considerable excess in the reaction.

Because of the preparative value of this reaction, it seemed desirable to extend this study to the higher homologous esters. The present paper reports the results which were obtained with ethyl valerate, caproate, heptoate, caprylate, pelargonate, caprate, laurate and myristate.

Each of these esters was condensed smoothly by sodium ethoxide to the corresponding keto ester in yields of 74–84% of the theoretical. It was not necessary to use an excess of the ester to remove the alcohol formed in the reaction since the higher boiling points of these esters allowed for the direct distillation of the alcohol from the reaction mixture without any appreciable loss of ester. Ethyl α-lauryl-laurate and ethyl α-myristylmyristate are solids and were purified by crystallization. The other β-keto esters are liquids at ordinary temperatures and consequently were purified by distillation. It was noticed that in the distillation of the keto esters derived from ethyl pelargonate and ethyl caprate small amounts of the corresponding ketones, pelargonone and caprinone, were obtained. These ketones resulted, presumably, from the pyrolysis of some of the keto ester during distillation, since it was found that carbon dioxide, ethylene, and carbon monoxide were evolved when each of these two keto esters was heated (at atmospheric pressure) to the temperature at which it distilled under diminished pressure. The β-keto esters were characterized by (a) the amount of carbon dioxide evolved on hydrolysis,[2] (b) the ketone produced by hydrolysis and (c) ultimate analyses. The carbon dioxide content of ethyl α-pelargonylpelargonate and ethyl α-caprylcaprate shows that considerable ketone is present in each of them. They were not purified further and consequently not analyzed. However, both of these impure β-keto esters gave excellent yields of the corresponding ketones on hydrolysis.

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[1] McElvain, THIS JOURNAL, **51**, 3124 (1929).

[2] Cope and McElvain, *ibid.*, **54**, 4322 (1932).

TABLE I

YIELDS AND PROPERTIES OF β-KETO ESTERS, $RCH_2COCH(R)COOC_2H_5$, AND KETONES, RCH_2COCH_2R

$RCH_2COCH(R)COOC_2H_5$											RCH_2COCH_2R	
							Calcd.		Found			
R is	Formula	Yields, %[a]	B. p. (mm.), or m. p., °C.	d^{25}_{25}	n^{25}_D	% CO_2	C	H	C	H	M. p., °C.[c]	Yield, %[d]
n-C_3H_7[e]	$C_{12}H_{22}O_3$	77	109–110 (5)	0.9330	1.4306	97.2	67.23	10.35	66.87	10.34	83 (22 mm.)[g]	72
n-C_4H_9	$C_{14}H_{26}O_3$	80	132–133 (5)	.9203	1.4351	97.0	69.36	10.82	69.00	10.77	14–15	81
n-C_5H_{11}[f]	$C_{16}H_{30}O_3$	78	147–148 (5)	.9107	1.4386	97.8	71.05	11.19	70.72	11.16	30–31	82
n-C_6H_{13}	$C_{18}H_{34}O_3$	84	173–175 (5)	.9047	1.4418	96.3	72.42	11.49	72.12	11.33	41–42	93
n-C_7H_{15}	$C_{20}H_{38}O_3$	74	195–200 (5)			91.9					52–53	93
n-C_8H_{17}	$C_{22}H_{42}O_3$	74	220–225 (5)			78.0					58–59	95
n-$C_{10}H_{21}$	$C_{26}H_{50}O_3$	79	28–29			96.3	76.38	12.10	76.00	12.11	68–69	98
n-$C_{12}H_{25}$	$C_{30}H_{58}O_3$	84	37–38			95.3	77.18	12.53	77.07	12.73	78–79	97

[a] These yields represent either distilled or recrystallized product.

[b] Obtained by hydrolysis of the keto ester.[2] Values above 95% are considered quantitative.

[c] The values reported in this column agree with those recorded in the literature for these ketones. The latter values are omitted for the sake of economy of space.

[d] Based on keto ester used.

[e] Reported by Israel, *Ann.*, **231**, 200 (1885), as having been obtained as a by-product in the reaction of sodium on ethyl propionate; however, the manner in which this compound was supposed to have been produced leaves considerable doubt in the minds of the authors as to its formation by such a reaction.

[f] Obtained by Hamonet, *Bull. soc. chim.*, [3] **2**, 339 (1889), through action of ferric chloride on oenanthyl chloride.

[g] Boiling point.

It should be emphasized that the extent to which the acetoacetic ester condensation of these higher esters takes place and the smoothness with which the resulting keto esters are hydrolyzed to the corresponding ketones make available an excellent method of preparation of higher ketones of the type, RCH_2COCH_2R.

The yields and properties of these β-keto esters and the corresponding ketones are summarized in Table I.

Experimental

Materials Used.—The esters which were used in the condensation were prepared by standard methods given in the literature and were thoroughly dried over anhydrous sodium sulfate and distilled before use. Sodium ethoxide was prepared from absolute alcohol and powdered sodium under dry ether.[3]

β-Keto Esters.—In a 125-cc. modified Claisen flask, with a fractionating side arm 35 cm. long, was placed 0.1 mole of the ester and 0.05 mole of sodium ethoxide. The reaction flask was attached to the receiving flask (which was not cooled) and this flask in turn was attached through a soda lime tower and a safety bottle to a manometer and a water pump. The safety bottle contained a stopcock which could be opened to the air and by which the pressure in the system could be regulated. The reaction flask was then heated carefully in an oil-bath to a temperature and under a pressure that caused a moderate, but not too vigorous, evolution of alcohol vapor as shown by the ebullition of the reaction mixture. The required temperature and pressure varied with the boiling point of the esters, the lower esters requiring lower reaction temperatures and higher pressures in order to prevent loss of ester. Consequently the time necessary for the completion of the reaction in these cases was increased. A summary of the conditions for the reaction of the various esters is given in Table II. Column 3 gives the temperatures and column 4 the pressures which were found to be most satisfactory at the beginning of each reaction to ensure a moderate evolution of alcohol. After the reaction had proceeded for some time these temperatures and pressures could be raised and lowered, respectively, without any appreciable loss of ester. Column 5 in Table II gives the time required for all of the alcohol to be evolved, *i. e.*, until the reaction mass ceased ebullition.

TABLE II

CONDITIONS AND TIME REQUIRED FOR FORMATION OF VARIOUS β-KETO ESTERS

Ester used, ethyl	B. p. of ester, °C. (mm.)	Reaction temp., °C.	Reaction pressure, mm.	Time for completion, hr.
Valerate	142–146 (750)	89–90	120–130	7–8
Caproate	57–60 (14)	90–95	75–80	7–8
Heptoate	75–79 (15)	90–95	60–65	7
Caprylate	94–99 (16)	90–95	20–25	5
Pelargonate	107–110 (15)	100–105	15–20	4–5
Caprate	118–121 (15)	105–110	15–20	4
Laurate	143–146 (15)	120–125	15–20	4
Myristate	167–170 (15)	125–130	15–20	4

The resulting reaction mixture was, at the temperature of reaction, a clear liquid with no visible particles of sodium ethoxide in suspension. The reaction products obtained from those esters above ethyl caprylate in molecular weight remained liquid after cooling to room temperature, but those derived from the lower molecular weight esters solidified to a clear, red transparent mass. The reaction product after cooling

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(3) Houben-Weyl, Vol. II, 1922, p. 578.

was treated with the calculated quantity of 30% acetic acid and shaken vigorously until the sodium salt had been completely decomposed. The keto ester was then extracted with 25 cc. of benzene and the resulting benzene solution, after washing with water, was dried over anhydrous sodium sulfate. The benzene was removed from the keto ester by distillation. Ethyl α-lauryl-laurate and ethyl α-myristylmyristate were recrystallized from absolute methanol. The other keto esters, being liquids, were purified by distillation. This procedure was quite satisfactory for all of the esters except ethyl α-pelargonylpelargonate and ethyl α-caprylcaprate, both of which suffered a small amount of pyrolysis to the corresponding ketone, which appeared as a low boiling, solid fraction in the distillation. These particular keto esters when heated at atmospheric pressure to the temperature at which they boiled under diminished pressure slowly evolved ethylene, carbon dioxide and carbon monoxide.

The properties of these keto esters are summarized in Table I.

Hydrolysis of the β-Keto Esters to Ketones.—The keto esters were hydrolyzed by refluxing for three to four hours with a 5% solution of potassium hydroxide in 90% alcohol. In the cases of valerone and caprone the alcohol was removed by distillation and the residue diluted with water, whereupon the liquid ketone layer separated. This was further purified by distillation. The higher ketones crystallized out from the alcoholic potassium hydroxide solution on cooling and after filtration were recrystallized from alcohol. The properties and yields of these ketones are listed in Table I.

Summary

The acetoacetic ester condensation has been applied to the synthesis of the following β-keto esters: ethyl α-valerylvalerate, ethyl α-caproylcaproate, ethyl α-heptoylheptoate, ethyl α-caprylylcaprylate, ethyl α-pelargonylpelargonate, ethyl α-caprylcaprate, ethyl α-lauryl-laurate, ethyl α-myristylmyristate.

Since these keto esters are readily hydrolyzed to the corresponding ketones, this procedure offers a most satisfactory method of preparation of the latter type of compounds.

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RECEIVED NOVEMBER 12, 1932
PUBLISHED APRIL 6, 1933