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Note

A General Method for the Synthesis of γ- and δ- Keto Esters

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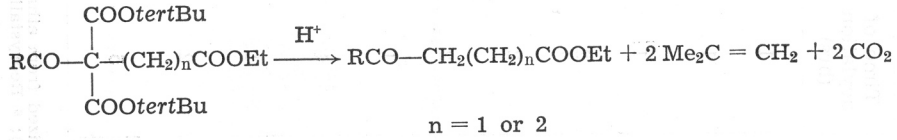
A method for the preparation of γ- and δ-keto esters is described. The sodio derivative of 1,1-di-*tert*-butyl-2-ethylethanetricarboxylate or 1,1-di-*tert*-butyl-3-ethylpropanetricarboxylate is acylated with a carboxylic acid chloride. Elimination of *tert*-butyl groups and decarboxylation are accomplished by heating the acylated triester in toluene with a catalytic amount of *p*-toluenesulphonic acid. Under these conditions the carbethoxy group remains unattacked.

A general method for the synthesis of γ- and δ-keto esters and keto acids, starting from 1,1-di-*tert*-butyl-2-ethylethanetricarboxylate and 1,1-di-*tert*-butyl-3-ethylpropanetricarboxylate[1] is described. This method is based on an earlier application of *tert*-butyl-ethyl malonate for the synthesis of β-keto esters[2] and di-*tert*-butyl malonates for the synthesis of ketones[3,4] and α-amino ketones[5].

The benzene solution of the mixed tricarboxylic ester when treated with sodium hydride and subsequently with an acid chloride, gave the acyl deri-



$$RCO{-}C(COO\,tert\,Bu)_2{-}(CH_2)_nCOOEt \xrightarrow{H^+} RCO{-}CH_2(CH_2)_nCOOEt + 2\,Me_2C{=}CH_2 + 2\,CO_2$$

$n = 1$ or 2

vative. This product, treated with a catalytic amount of *p*-toluenesulphonic acid in boiling toluene undergoes thermal decomposition to keto ester. Sometimes besides the keto ester a small amount of the keto acid is obtained. To avoid this side reaction absolute ethanol is added to the toluene solution and after the ketonic cleavage the boiling is continued for about 2—3 hours. When the ketonic cleavage is carried out in the presence of an equimolar quantity of *p*-toluenesulphonic acid, the keto acid is produced.

EXPERIMENTAL

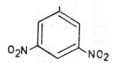
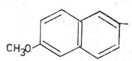
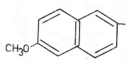
Melting points were determined on a Kofler heating microscope.

General Procedure

Sodium hydride (0.72 g., 0.03 mole), the requisite mixed triester (0.02 mole) and dry benzene (60 ml.) are heated to reflux and stirred for about 3 hours under exclusion of moisture. Then 0.02 mole of acid chloride in 40 ml. of dry benzene is

TABLE I

$R-CO-(CH_2)_n-COOC_2H_5$

Compound	R	n	Time of acylation (hrs)	Yield %	m. p. °C or b. p. °C/mm	Formula	Calc'd. Found % C	Calc'd. Found % H	Calc'd. Found % N	Corresponding acid m. p. °C
I		3	1	87	57—58[a]					
II		2	1	85	75[b]	$C_{13}H_{13}NO_3$	67.52 67,18	5.67 5.50	6.06 6.34	
III		3	1	90	106—107[b]	$C_{13}H_{14}N_2O_7$	50.32 50.21	4.55 4.32	9.03 9.13	
IV		2	2	71	47[b,c]					171—172[b,i]
V		2	2	75	108—109[b,d]					146—147[b,i]
VI		3	2	80	93.5—94[b,e]					172—174[b,i]
VII		3	1	71	147—153/0.6	$C_{12}H_{15}NO_3$	65.14 64.82	6.83 6.93	6.33 5.99	127—128[g,h]
VIII		2	1	82	140—146 0.2	$C_{11}H_{13}NO_3$	63.75 63.55	6.32 6.45	6.76 6.82	185[g,h]
IX		3	1	78	153—155/0.4	$C_{12}H_{15}NO_3$	65.14 64.85	6.83 7.12	6.33 6.89	197—199[g,h]
X		3	2	75	48—49[f]	$C_{16}H_{17}NO_3$	70.83 70.47	6.32 6.09	5.16 5.30	129—130[g,h]
XI		3	5	73	103—105[f]	$C_{18}H_{23}NO_6S$	56.69 56.31	6.07 6.28	3.67 3.93	186—187[g,h]

[a] Reported[6] m. p. 58.5—59; [b] Recrystallized from ethanol; [c] Reported[7] m. p. 47—48; [d] Reported[8] m. p. 105.5—106.5; [e] Reported[9] m. p. 94.5—95; [f] Recrystallized from diluted ethanol (1 : 1); [g] Recrystallized from water; [h] Reported[10]; [i] Reported[11].

added and heating with stirring is continued for 1—2 hours. If the acylation is carried out with an unreactive acid chloride, heating must be prolonged for several hours. The mixture is cooled to room temperature, 0.6 g. (0.01 mole) of glacial acetic acid is added to destroy the excess of sodium hydride and the precipitate is removed by filtration. Benzene is evaporated *in vacuo* and the residual acyl malonate is dissolved in 100 ml. of toluene and heated to reflux with 0.25 g. of *p*-toluenesulphonic acid. If the acyl malonate contains a basic nitrogen heterocyclic ring, 3.7 g. of *p*-toluenesulphonic acid must be added. Refluxing is continued until gas evolution stops (about 2—3 hours). Then, 20 ml. of absolute ethanol is added and the mixture is warmed for 2 hours. After cooling, excess of 20% potassium carbonate is added and stirring is continued for 10 minutes. Then the toluene layer is washed with water and dried. After the removal of solvent, the resulting material is purified by distillation or crystallization.

In this manner the keto esters I—XI and the keto acids listed in Table I, were prepared.

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IZVOD

Opšta metoda za sintezu γ- i δ-keto-estara

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Data je opšta metoda za sintezu γ- i δ-ketoestara u kojoj se polazi od 1,1-di-*t*-butil-2-etil-etantrikarboksilata ili 1,1-di-*t*-butil-3-etil-propantrikarboksilata. Natrijum derivat mešovitog triestra aciluje se hloridom kiseline i dobiveni acil derivat zagreva u toluenu u prisustvu nešto *p*-toluensulfonske kiseline, pri čemu se razlažu obe karbo-*t*-butoksi grupe. Proizvod reakcije je γ- ili δ-ketoestar. Ako se ovo razlaganje izvodi u prisustvu ekvimolarne količine *p*-toluensulfonske kiseline, onda se dobija γ- ili δ-ketokiselina. Metoda je pogodna i za dobivanje ketoestara sa piridinskim ili hinolinskim prstenom.

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