70. *Experiments on the Synthesis of Carbonyl Compounds. Part I. Introduction. The Acidolysis of Acylmalonic Esters.*

By R. E. Bowman.

The initial aims of the present series of papers are outlined. Acid-catalysed acidolysis of acylmalonic esters (IV) is shown to furnish the methyl ketones (VI) in high yield. Conditions have been found for the isolation of the intermediate *β*-keto-esters (V) in moderate yields.

Despite comparatively recent developments such as the use of cadmium dialkyls (Cason, *Chem. Reviews*, 1947, **40**, 15) and the general β-keto-ester synthesis devised by Breslow, Baumgarten, and Hauser (*J. Amer. Chem. Soc.*, 1944, **66**, 1286) a number of the more complex polyfunctional types of carbonyl compounds remain inaccessible. Whilst there can be little doubt that the method employing organo-cadmium compounds is convenient for preparing the simpler types of ketones, its general application is inevitably limited by the usual restrictions accompanying the use of Grignard reagents; on the other hand, methods involving the use of β-keto-esters are frequently unsatisfactory owing to low yields at one or more of the many stages involved, *viz.*, the synthesis of the β-keto-esters, mono- or di-alkylation, and eventual ketonic hydrolysis, sometimes under severe conditions (Renfrow, *J. Amer. Chem. Soc.*, 1944, **66**, 144).

Examination of the problem of developing a more general method suggested that a promising route lay in the simple metathetical reaction between acid chlorides and sodiomalonic esters, provided that the degradation of the β-keto-diester (I) could be realised.

$$\text{R·COCl} + \text{R}'\text{·CNa(CO}_2\text{Et}_2)_2 \longrightarrow \underset{\text{(I.)}}{\text{R·CO·CR}'(\text{CO}_2\text{Et})_2} \longrightarrow \text{R·CO·CH}_2\text{R}'$$

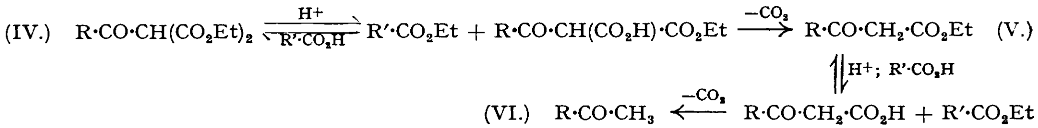
Compounds (I) have been prepared on various occasions during the last fifty years but have rarely been used in synthetical operations owing to the ease with which they suffer disruption into their original components (except where R′ = H) under the action of the normal hydrolytic reagents (Michael, *Amer. Chem. J.*, 1892, **14**, 510; Robinson and Robinson, *J.*, 1925, **127**, 175). The problem, therefore, resolved itself into that of finding conditions for generating the free acylmalonic acids from their esters whilst leaving intact the rest of the molecule, spontaneous or subsequent thermal decarboxylation of the keto-acid (II) to the ketone (III) being expected to occur quantitatively.

$$\text{(I)} \longrightarrow \underset{\text{(II.)}}{\text{R·CO·CR}'(\text{CO}_2\text{H})_2} \longrightarrow \underset{\text{(III.)}}{\text{R·CO·CH}_2\text{R}'} + 2\text{CO}_2$$

This and the subsequent paper report two different approaches to this problem, and in both cases new methods of ketone synthesis have been elaborated. Experiments on the removal of one carbethoxy-group from acylmalonic and the analogous acylcyanoacetic esters, with the object of obtaining β-keto-esters and β-keto-nitriles respectively, will be reported later.

Acidolysis of Acylmalonic Esters.—Acylmalonic esters (IV) are, in general, high-boiling, viscous liquids or low-melting solids existing mainly in the enolic form and hence readily soluble in aqueous alkalis, in which media they are readily hydrolysed to their progenitors (Michael, *loc. cit.*). Therefore, use of alkaline conditions to bring about ketonic hydrolysis offers little hope of success. In recent years, however, the required degradation has been realised by several groups of workers (Giacolone, *Gazzetta*, 1936, **65**, 1127; Adickes, *J. pr. Chem.*, 1943, **161**, 271; Fuller, Tonkin, and J. Walker, *J.*, 1945, 633; H. G. Walker and Hauser, *J. Amer. Chem. Soc.*, 1946, **68**, 1386) employing strong acids. The technique developed by Walker and Hauser, whereby the crude acylmalonic esters prepared from the acid chloride and ethoxymagnesiomalonic ester (Lund, *Ber.*, 1934, **67**, *B*, 935) are subjected to boiling aqueous sulphuric acid in acetic acid solution, has been shown to be extremely useful for the preparation of ketones $\mathrm{R{\cdot}CO{\cdot}CH_3}$ where R is aromatic; the reaction failed completely when R was a straight-chain alkyl group such as *n*-amyl and for the fully substituted compounds (I; $\mathrm{R = NO_2{\cdot}C_6H_4}$, $\mathrm{R' = Bu^n}$).

It seemed possible that a more general solution to this problem might be realised by the use of acid-catalysed acidolysis according to the following scheme:



$$\begin{array}{c}
\text{(IV.)}\quad \mathrm{R{\cdot}CO{\cdot}CH(CO_2Et)_2} \underset{\mathrm{R'{\cdot}CO_2H}}{\overset{\mathrm{H^+}}{\rightleftharpoons}} \mathrm{R'{\cdot}CO_2Et} + \mathrm{R{\cdot}CO{\cdot}CH(CO_2H){\cdot}CO_2Et} \xrightarrow{-\mathrm{CO_2}} \mathrm{R{\cdot}CO{\cdot}CH_2{\cdot}CO_2Et}\quad \text{(V.)} \\
\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad \Big\downarrow\!\Big\uparrow\ \mathrm{H^+;\ R'{\cdot}CO_2H} \\
\qquad\qquad\qquad \text{(VI.)}\quad \mathrm{R{\cdot}CO{\cdot}CH_3} \xleftarrow{-\mathrm{CO_2}} \mathrm{R{\cdot}CO{\cdot}CH_2{\cdot}CO_2H} + \mathrm{R'{\cdot}CO_2Et}
\end{array}$$

The initial experiments were carried out by refluxing a mixture of benzoylmalonic ester (1 mol.) and acetic acid (8 mols.) containing 1% sulphuric acid as catalyst. The expected reaction was found to occur with evolution of carbon dioxide and formation of acetophenone, benzoylacetic ester, and some unchanged starting material. Although the isolation of some β-keto-ester was highly satisfactory, attention at this stage of the work was focussed on the problem of forcing the reaction to completion. Substitution of propionic acid for acetic acid led to a considerable improvement in the yield of ketone although a small quantity of β-keto-ester still remained. Finally the technique of refluxing the acylmalonic ester (1 mol.) with propionic acid (5—8 mols.) and sulphuric acid (1% by weight of reactants) for 3 hours, followed by a short treatment with 10N-sulphuric acid to complete the hydrolysis of any residual β-keto-ester, was adopted. In this manner benzoylmalonic ester yielded acetophenone in practically quantitative yield.

Nevertheless, the isolation of the acylmalonic esters was both wasteful of materials and restrictive in scope in view of the high boiling points of even the lower members of the series and hence conditions were sought for obtaining the highest possible yield of crude acylmalonic esters. The technique employed by Walker and Hauser (*loc. cit.*) suffers from the disadvantage that the reaction is carried out in the presence of free ethanol employed in the formation of the magnesium derivative. It seemed that the presence of the latter, together with that inevitably formed in the reaction, would considerably lower the yield of keto-ester, particularly in the aliphatic series. The preparation of ethoxymagnesiomalonic ester was therefore effected in benzene solution, using only a slight excess of ethanol which was finally removed as its azeotrope with benzene; in this manner ethanol-free solutions of the magnesium complex were readily obtained. Treatment of this reagent (100% excess) with the requisite acid chloride, followed by recovery of excess of malonic ester by distillation, yielded the crude keto-diester which on acidolysis as above furnished the methyl ketone $\mathrm{R{\cdot}CO{\cdot}CH_3}$ in very high yield.

In this manner the acid chlorides of octanoic, undecanoic, dodecanoic, stearic, sebacic, *o*-chlorobenzoic, and *p*-nitrobenzoic acids, and of methyl hydrogen sebacate gave the corresponding methyl ketones. Even in the aromatic series, as shown by the last two examples, the yields by this process are considerably higher than those obtained by Walker and Hauser (*loc. cit.*).

Preparation of β-keto-esters from the corresponding acylmalonic esters was first described by Bernhard (*Annalen*, 1894, **282**, 166) who obtained benzoylacetic ester by steam-distillation of benzoylmalonic ester. Breslow *et al.* (*loc. cit.*) obtained propionylacetic ester similarly but in very poor yield. Recently, two new methods have been elaborated; first, the general β-keto-ester synthesis of Breslow *et al.* (*ibid.*) using the rather inaccessible ethyl *tert.*-butylmalonate, and, secondly, thermal pyrolysis of acylmalonic esters in the presence of toluene- or naphthalene-sulphonic acid (Riegel and Lilienfield, *J. Amer. Chem. Soc.*, 1945, **67**, 1274).

The isolation of some of the intermediate β-keto-ester in the early experiments on the acidolysis of benzoylmalonic ester raised hopes that it might be possible to find conditions for obtaining the analogous aliphatic keto-esters. For this purpose a large quantity of lauroylmalonic ester was prepared and submitted in portions to the action of acetic acid (1 : 5) with various quantities of catalyst for various times. Limitation of time prevented a full examination of the reaction but under the best conditions found (3 hours at the boiling point using 0·22% sulphuric acid), a 48% yield of lauroylacetic ester (V; $\mathrm{R = C_{11}H_{23}}$) and a 41% yield of the ketone (VI; $\mathrm{R = C_{11}H_{23}}$) were obtained. A similar reaction applied to undec-10-enoyl chloride furnished *ethyl 3-ketotridec-12-enoate* * (V; $\mathrm{R = CH_2{:}CH{\cdot}[CH_2]_8}$) (45%) and the ketone (VI; $\mathrm{R = CH_2{:}CH{\cdot}[CH_2]_8}$) (41%). The reaction was finally investigated on a larger scale (1·25 mols.) using octanoyl chloride, ethyl 3-ketodecanoate (V; $\mathrm{R = C_7H_{15}}$) (43%) together with methyl heptyl ketone (VI; $\mathrm{R = C_7H_{15}}$) (52%) being obtained.

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* Geneva nomenclature is used throughout this paper.

Finally the acidolysis of fully substituted acylmalonic esters (I; R = R′ = alkyl) was investigated, but in no case could the desired reaction be brought about. The failure of Renfrow (*loc. cit.*) to bring about a similar reaction with fully substituted β-keto-esters, $\mathrm{CH_3{\cdot}CO{\cdot}CRR'{\cdot}CO_2Et}$, may be significant in this connexion. In the course of this work *ethyl* n-*butyl* iso*hexoylmalonate* (*6-keto-9-methyldecane-5 : 5-dicarboxylate*) (I; R = $\mathrm{(CH_3)_2CH{\cdot}CH_2{\cdot}CH_2}$, R′ = $\mathrm{Bu^n}$) was prepared.

EXPERIMENTAL.

Ethoxymagnesiomalonic Ester.—Magnesium (36 g., 1·5 mols.) was covered with dry benzene (110 ml.) containing absolute ethanol (10 ml.) in a three-necked flask fitted with a tap funnel and reflux condenser. After the addition of a crystal of iodine and/or carbon tetrachloride (1 ml.) a small portion of a solution (*A*) of ethyl malonate (commercial, undistilled; 240 g., 1·5 mols.), absolute ethanol (70 g., *i.e.*, 78 g. in all; 1·7 mols.) in dry benzene (300 ml.) was added and the mixture heated, if necessary, until a vigorous reaction set in. Solution (*A*) was then added at a convenient rate (2—3 hours) and the product refluxed until dissolution of the magnesium was complete. At this stage the reflux condenser was replaced by a fractioning column of the Widmer or Fenske type (30 cm. long) fitted with a reflux head, and the mixture was slowly distilled until most of the free ethanol had been removed as azeotrope with benzene (b. p. 68·4°) as shown by a tendency for the distillation temperature to rise to about 70°. The residue in the flask consisted of ethanol-free ethoxymagnesiomalonic ester in benzene solution (volume, approx. 700 ml.) and was ready for use.

Crude Acylmalonic Esters.—The requisite acid chloride (1 mol.) in dry benzene was added, with stirring and external cooling, to the benzene solution of ethoxymagnesiomalonic ester (2 mols.) during 30 minutes and the resulting mixture refluxed for 1 hour. The cooled solution was decomposed by addition to ice and dilute sulphuric acid, and the organic layer thoroughly shaken with more dilute sulphuric acid, followed by water (3 portions). Removal of the first portion of benzene from the dried solution ($\mathrm{Na_2SO_4}$) was effected at room temperature under reduced pressure. The excess of malonic ester was then recovered by distillation at 0·5 mm. (bath-temperature up to 100°), in excellent yield. A fractionating column was not necessary at this stage when acids higher than heptanoic acid were used.

Complete Acidolysis.—A mixture of the crude acylmalonate (1 mol.), propionic acid (commercial; 8 mols.), and sulphuric acid (1% by weight of total weight of reactants) was boiled under reflux for 3 hours; a vigorous evolution of gas occurred in the early stages. Then sulphuric acid (75 ml. of 4N.) was added to the slightly cooled reaction mixture, and refluxing was continued until no further gas was evolved. The method of working up depended on the scale of the reaction and nature of the product.

Method A (*small scale*). The reaction product was poured into water, and the mixture neutralised by aqueous sodium hydroxide. The ketone, if solid, was then filtered off or, if liquid, taken up in a solvent and isolated in the usual manner. If the product was a keto-acid, it was extracted directly without neutralisation.

Method B (*small scale; non-volatile ketones*). The reaction mixture was poured into water, and steam passed into the mixture until the propionic acid was all removed. The product was then isolated from the residue as usual.

Method C (*large scale*). An excess (70% over that required for neutralisation of the sulphuric acid) of anhydrous sodium acetate was added to the acidolysis mixture which was then distilled under reduced pressure through a Vigreux column (20 cm. long) to remove ethyl propionate and most of the propionic acid. The residue was then worked up as described in method (A).

In this manner the following acid chlorides were converted into the respective methyl ketones.

Starting materials.		Ketone, $\mathrm{R{\cdot}CO{\cdot}CH_3}$.			
Acid.	Acid chloride. B. p. or m. p.	R.	Method.	B. p. or m. p.	Yield, %.
Octanoic	82°/15 mm.	*n*-Heptyl [1]	(C)	80°/10 mm.	93
Undecanoic	95°/15 mm.	*n*-Decyl [2]	(A)	107°/5 mm.	94
Lauric	136°/10 mm.	*n*-Undecyl [3]	(A)	27—28°	97
Stearic [4]	—	*n*-Heptadecyl [5]	(B)	55—56°	96
Sebacic	140°/1 mm.	*n*-9-Ketodecyl [6]	(A)	69°	93
Methyl hydrogen sebacate [7]	—	ω-Carboxyoctyl [9]	(B)	56°	100 [8]
o-Chlorobenzoic	90°/10 mm.	*o*-Chlorophenyl [10]	(A)	84°/3 mm.	98
p-Nitrobenzoic	72°	*p*-Nitrophenyl [12]	(B)	75—78°	99 [11]

[1] Semicarbazone, m. p. 117—118° (Dakin, *Amer. Chem. J.*, 1910, **44**, 46, reported m. p. 118°)

[2] Semicarbazone, m. p. 122—123° (Pickard and Kenyon, *J.*, 1911, **99**, 57, gave m. p. 122—123°).

[3] Semicarbazone, m. p. 117° (Ruzicka, Stoll, and Schinz, *Helv. Chim. Acta*, 1928, **11**, 685, and Asahina and Nakayama, *J. Pharm. Soc. Japan*, 1925, **52**, 65, gave m. p.s 115—116° and 118—119° respectively).

[4] Crude: prepared from the acid and thionyl chloride, with removal of the latter *in vacuo*.

[5] Oxime, m. p. 77° (Thoms and Vogelsang, *Annalen*, 1907, **357**, 161, reported m. p. 77°).

[6] Dodecane-2 : 11-dione, slender needles [from light petroleum (b. p. 40—60°)], m. p. 69° (Cason and Prout, *J. Amer. Chem. Soc.*, 1944, **66**, 46, reported m. p. 67·4—67·8°) (Found: C, 72·4; H, 10·8. Calc. for $\mathrm{C_{12}H_{22}O_2}$: C, 72·7; H, 11·1%). The *dioxime* crystallised from ethyl acetate and then benzene in prisms, m. p 114—115° (Found: N, 11·9. $\mathrm{C_{12}H_{24}O_2N_2}$ requires N, 12·3%).

[7] *Org. Synth.*, 1945, **25**, 71.

[8] Crude.

[9] Crystallised from benzene; m. p. 58° (Abraham, Mowat, and Smith, *J.*, 1937, 948, gave m. p. 59°); semicarbazone, m. p. 135° (*idem, ibid.*, m. p. 135—136°).

[10] Semicarbazone, m. p. 159° (Wahl and Rolland, *Ann. Chim.*, 1928, [x], **10**, 29, reported m. p. 159—160°).

[11] Crude.

[12] Crystallised from benzene–light petroleum (b. p. 40—60°); m. p. 80° (Drewsen, *Annalen*, 1882, **212**, 160, gave m. p. 80—81°); oxime, m. p. 172° (Posner, *ibid.*, 1912, **389**, 43, gave m. p. 172—173°).

Partial Acidolysis. Preparation of β-Keto-esters.—The following conditions gave the best results: The crude acylmalonate (as above; 1 mol.), glacial acetic acid (5 mols.), and sulphuric acid (0·22% by weight of reactants) were boiled under reflux for 3 hours. Excess of barium carbonate (5 times the wt. of sulphuric acid) was then added to the cooled reactants, and the mixture set aside with occasional agitation for 1 hour. After filtration, the filtrate was carefully fractionated *in vacuo* in the presence of a trace of barium carbonate, through a Vigreux column.

Ethyl 3-*Ketotetradecanoate.*—In this manner lauroylmalonic ester (crude; 0·1 mol.) gave methyl undecyl ketone, b. p. 110—112°/5 mm. (8·7 g., 44%), and the keto-ester as a colourless oil, b. p. 128—130°/0·2 mm., n_D^{20} 1·4489 (13 g., 48%) (Found: C, 70·6; H, 10·8. Calc. for $C_{16}H_{30}O_3$: C, 71·1; H, 11·1%). The latter ester gave a deep-red ferric reaction and formed a *pyrazolone* which separated from methanol and then light petroleum (b. p. 40—60°) in colourless prisms, m. p. 67° (Found: N, 11·0. $C_{20}H_{30}ON_2$ requires N, 10·8%).

Ethyl 3-*Ketodecanoate.*—Crude octanoylmalonic ester (1·25 mols.) similarly furnished methyl heptyl ketone (93 g., 52%) and the keto-ester as a colourless oil, b. p. 84—86°/0·2 mm., n_D^{20} 1·4390, which gave a deep-red colour with aqueous-alcoholic ferric chloride (Found: C, 66·8; H, 10·0. Calc. for $C_{12}H_{22}O_3$: C, 67·3; H, 10·4%) (yield: 112 g., 43%). The pyrazolone separated from methanol and then light petroleum (b. p. 40—60°) in colourless prisms, m. p. 82° (Breusch and Keskin, *Rec. Fac. Sci. Univ. Istanbul*, 1946, **11**, *A*, 24, reported m. p. 82°) (Found: N, 9·0. Calc. for $C_{16}H_{22}ON_2$: N, 8·9%).

Ethyl 3-*Ketotridec*-12-*enoate.*—Undec-10-enoyl chloride (b. p. 98°/3 mm.; 41 g., 0·2 mol.) was treated with ethoxymagnesiomalonic ester (0·4 mol.), and the crude product partly acidolysed according to the general method. In this manner, dodec-11-en-2-one (15 g., 41%), b. p. 104°/5 mm. (semicarbazone, m. p. 122—123°), and *ethyl* 3-*ketotridec*-12-*enoate*, a colourless oil (23 g., 45%), b. p. 122—124°/0·4 mm., n_D^{20} 1·4485 (Found: C, 70·5; H, 10·6. $C_{15}H_{26}O_3$ requires C, 70·9; H, 10·2%), were obtained. The latter gave a deep-red ferric colour and formed a *copper* derivative which separated from ice-cold light petroleum (b. p. 40—60°) in pale green, slender needles, m. p. 75—77° [Found: Cu, 10·9. $Cu(C_{15}H_{25}O_3)_2$ requires Cu, 11·2%].

Ethyl 6-*Keto*-9-*methyldecane*-5 : 5-*dicarboxylate.*—Prepared in the usual manner (cf. Michael, *loc. cit.*) from *iso*hexanoyl chloride and sodio-*n*-butylmalonic ester in ether, the *ester* was obtained as a colourless viscous oil, b. p. 120°/0·5 mm., n_D^{20} 1·4408 (Found: C, 64·9; H, 9·7. $C_{17}H_{30}O_5$ requires C, 65·0; H, 9·8%).

BIRKBECK COLLEGE, LONDON, E.C.4.

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