

A similar substance even seems to be present in bovine serum, and it can be separated from serum protein by dialysis.

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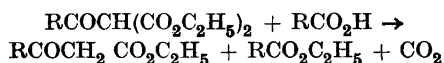
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### A Disregarded Complication in the Synthesis of $\beta$ -Ketoesters by the Base Catalysed Acidolysis of Diethyl Acylmalonates

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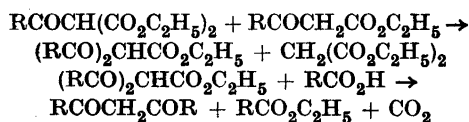
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The author has recently described a method for preparing  $\beta$ -ketoesters using a base catalysed acidolysis of diethyl acylmalonates according to the following equation<sup>1</sup>:



This reaction was found to give mixtures of  $\beta$ -ketoesters if the acyl group of the acid was not the same as that of the acylmalonate used<sup>2</sup>.

This fact and some other observations have called my attention to the possibility that the  $\beta$ -ketoesters obtained are not quite pure even if both the acyl groups are the same. The main impurities resulting from the acyl group mobility<sup>2</sup> would be the corresponding  $\beta$ -diketone and diethyl malonate. The reaction leading to these products probably is:



In my first preparation of ethyl propionylacetate the possibility of an impurity in the form of diethyl malonate was fully

realised and a test according to Breslow, Baumgarten, and Hauser<sup>3</sup> was made for this compound. This test was negative. These authors stated, that the complete solubility of the product in 5 % sodium hydroxide will show the absence of any appreciable quantities of diethyl malonate. However, such a statement is false as diethyl malonate itself is readily soluble in 5 % sodium hydroxide. Later experiments have shown, indeed, that the product was contaminated by appreciable quantities of diethyl malonate and dipropionylmethane.

It can be demonstrated that the ethyl diacetylacetate is a probable intermediate product since ethyl diacetoacetate can be isolated in appreciable quantities from the reaction of diethyl acylmalonate and ethyl acetoacetate.

The second step in the reaction, the acidolysis of the ethyl diacetylacetate with an organic acid is a well-known reaction for the preparation of  $\beta$ -diketones<sup>4-6</sup>.

In order to see the extent to which these side reactions have proceeded in the preparations of the  $\beta$ -ketoesters reported in the previous publication, the products have been tested for the diketone and the diethyl malonate.

The synthesis of ethyl propionylacetate was repeated on a 2 mole scale. When the product was carefully fractionated through a very efficient Pyrex Widmer column, a forerun of 47 g b.p. 40–68°/7.5 mm was obtained. This fraction was precipitated with a solution of copper acetate, yielding the copper derivative of dipropionylmethane m.p. 212° corresponding to 31 g of dipropionylmethane b. p. 59°/9 mm, or a 12 % yield based on the diethyl propionylmalonate.

The forefraction was followed by a fraction boiling at 68–69°/7.5 mm and a fraction at 72–73°/7.5 mm together with a very small middle fraction b.p. 69–72°/7.5 mm. A determination of the refractive indices of the two main fractions showed that the low boiling product had a somewhat higher

initial value  $n_D^{20} = 1.4351$  than the high-boiling one, but this value rapidly decreased to that of the latter, viz.  $n_D^{20} = 1.4315$ . No attempts were made to obtain the highest value of the refractive index for the low-boiling product, but it is obvious that the two products are the enol- and keto-forms of ethyl propionylacetate.

The residue in the distillation flask consisted of diethyl malonate b.p. 79–81°/7.5 mm amounting to about 10 % of the initial product, together with a small quantity of high-boiling products.

From this experiment it is obvious that the reaction does not give a pure product, but that the mixture can be separated to give ethyl propionylacetate in a rather good yield (over 50 %). This seems at present to be the best method of preparing this compound.

The product obtained from the reaction of isobutyric acid with diethyl isobutyrylmalonate was carefully fractionated. In this way a very small forerun b.p. 50–72°/8 mm was obtained, followed by an absolutely constant boiling fraction 74.4°/7.5 mm leaving a very small residue. From the forerun diisobutyrylmethane was isolated in the form of its copper derivative in a yield of about 1 %. M.P. (after recrystallisation) 124°. This indicates that the reaction gives a rather pure product in this case. The method is, no doubt, the best one of preparing ethyl isobutyrylacetate.

In the preparation of ethyl *n*-butyrylacetate by the reaction of *n*-butyric acid with diethyl *n*-butyrylmalonate a very troublesome mixture is obtained as the boiling-points of all the three main products are in the region 198–203°. In this case a separation by distillation is quite impossible. In order to test the product for impurities 10 g of the distilled product were refluxed with 100 ml of 20 % sulphuric acid for 3 hours and the product then steam distilled. This treatment decomposes all components except the dibutyrylmethane, which was precipitated in the form of the

copper derivative m.p. 157° in a yield of 11 %. As the product must contain a corresponding quantity of diethyl malonate it will be only about 78 % pure. It may be pointed out that as the product is entirely free from homologues it may be very useful in the preparation of certain derivatives where the contamination of diethyl malonate and dibutyrylmethane is harmless.

In order to prove the existence of ethyl diacetylacetate as an probable intermediate in the formation of the diketone, a mixture of equimolar amounts of diethyl acetylmalonate and ethyl acetoacetate were refluxed with a little magnesium oxide and copper acetate as a catalyst. After three hours heating the mixture was fractionated under reduced pressure. From a 0.2 mole run the following fractions were taken: (I) 30–60°/7.5 mm 3 g, (II) 60–75°/7.5 mm 6 g, (III) 75–83°/7.5 mm 22 g, (IV) 83–100°/7.5 mm 10 g, together with a considerable quantity of high-boiling products. From fraction (I) a little (1.5 g) acetylacetone was isolated as the copper derivative. Fraction (II) consists no doubt of unchanged ethyl acetoacetate. Fraction (III) gives on redistillation a fraction b.p. 79–81°/7.5 mm which is diethyl malonate. *S*-Benzyl-isothiuronium salt m.p. 147°. From fraction (IV) ethyl diacetoacetate was isolated in the form of the copper derivative, m.p. 152°, (5.7 g). The formation of acetylacetone is presumably a result of secondary reactions consequent from the high temperature employed.

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