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

The Preparation of Ethyl α-Carbethoxy-α′-isobutyryl-β-phenylglutarate. Some Observations on the Retrogression of the Michael Reaction

BY EDWIN H. KROEKER AND S. M. MCELVAIN

In the course of a study of the acetoacetic ester condensation it became necessary to prepare ethyl α-carbethoxy-α′-isobutyryl-β-phenylglutarate (III). Dieckmann and Kron's condensation[1] of benzalmalonic ester (I) and isobutyrylacetic ester (II) to 2,2-dimethyl-5-phenyl-4,6-dicarbethoxy-cyclohexadione-1,3 (IV) undoubtedly went through III (reactions A and C) but no attempt was made in their work to isolate this intermediate compound.

In order that the internal acetoacetic ester condensation of III (reaction C) might be prevented, a study of the Michael reaction (A) in the presence of a minimum amount of sodium ethoxide was undertaken. When one molecular equivalent each of I and II were allowed to react for thirty-two hours in the presence of 0.1 equivalent of sodium ethoxide, three distinct fractions were obtained when the reaction mixture was carefully fractionated. The lowest boiling fraction (85–90° (15 mm.)) boiled at about the same temperature as isobutyrylacetic ester (II), but on closer inspection it was found that this fraction was a mixture of II and malonic ester (V). The intermediate fraction boiled at 149–153° (3 mm.), approximately the boiling point of benzalmalonic ester (I). A rather low yield (22% calculated as III) of the high boiling (188–193° (3 mm.)) fraction was obtained. The presence of malonic ester in the low boiling fraction indicated that III had undergone the retrogression indicated by reaction B. Since α-isobutyrylcinnamic ester (VI) boils at about the same temperature as benzalmalonic ester, it was contained in the intermediate fraction. The presence of malonic ester in the reaction mixture was the cause of a further complication in that it reacts with I to form ethyl α,α′-dicarbethoxy-β-phenylglutarate (VII), a product which boils (184–188° (3 mm.)) within the range of III. In fact carbon and hydrogen analyses and the molecular refraction of the high boiling fraction obtained under these conditions (run 1, Table I) indicated that it contained 38–48% of VII and 52–62% of III.

(1) Dieckmann and Kron, *Ber.*, **41**, 1260 (1908).

TABLE I

REACTION PRODUCTS FROM 1 MOLE EACH OF BENZALMALONIC ESTER AND ISOBUTYRYLACETIC ESTER[a]

Run	Reaction time, hr.	Mole of V	Mole of II[b]	Mole of I and VI[c]	Mole of III[d]
1	32	0.13	0.21	0.46	0.22
2	1	.09	.04	.16	.65
3	0.33	.05	.11	.22	.46
4	0.10	.13	.51	.72	.05

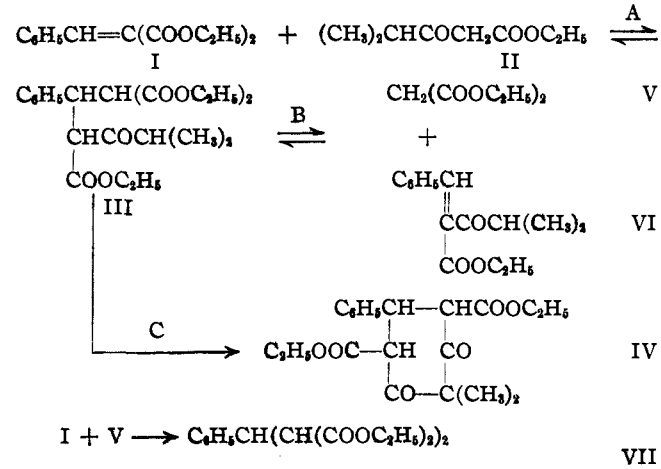
[a] Each value reported in this table was checked by a duplicate run.

[b] The values in this column together with the corresponding values in the preceding column represent the total yield of the low boiling (85–90° (15 mm.)) fraction.

[c] The intermediate boiling (149–153° (3 mm.)) fraction. Since the components of this fraction (I and VI) have practically the same molecular weight and boiling points it is not necessary to know their relative amounts in order to estimate the sum of their molecular quantities. Theoretically the sum of the moles of I and VI should equal the sum of the moles of V and II.

[d] The high boiling (188–193° (3 mm.)) fraction. Calculated as compound III. The product from run 1 was found by analyses to contain 38–48% of VII, but from runs 2, 3 and 4 it was found to be practically pure III.

In the hope of eliminating these undesired reactions the reaction time was drastically reduced. The yields of the various fractions which were obtained together with the amounts of each of the components (II and V) of the low boiling fraction are summarized in Table I. The estimation of these components is described in detail in the experimental part.



It is seen from the data in Table I that about one hour is the optimum reaction time for the production of the maximum yield of III (run 2), but in run 4, even though a relatively small amount of III was obtained, analysis of the low boiling fraction showed the presence of a considerable amount of malonic ester (V). These values would indicate that reaction A had taken place to the extent of 18% while B had taken place to the extent of 13%.

The apparent speed of reaction B and the consequent piling up of malonic ester in the reaction mixture suggested the preparation of III from V and VI. A summary of the results obtained from a series of runs is given in Table II.

TABLE II

REACTION PRODUCTS FROM 1 MOLE EACH OF MALONIC ESTER AND α-ISOBUTYRYLCINNAMIC ESTER[a]

Run	Reaction time, hr.	Mole of V	Mole of II	Mole of I and VI	Mole of III
1	1	0.23	0.29	0.78	0.15
2	0.5	.24	.18	.53	.30
3	0.1	.06	.08	.11	.72

[a] The explanatory footnotes of Table I are applicable to Table II.

The results summarized in Table II show that the highest yield of III is obtained after about six minutes of reaction, and that after this time the retrogression reaction sets in rapidly.

The data in Tables I and II indicate quite definitely that the successful preparation of III is dependent upon the regulation of the reversible reactions A and B. Since malonic ester adds to VI about ten times faster than isobutyrylacetic ester adds to I (*cf.* run 3, Table II with run 2, Table I) it is obvious that the compounds V and VI offer the better approach to III. In fact, it appears from run 4 of Table I that the retrogression of III into V and VI is so much faster than the formation of III from I and II that even though the latter pair of products is used in the reaction, III is really formed in considerable part, through the recombination of its retrogression products V and VI. Although the retrogression of III into I and II takes place extensively after 0.1 hr. (runs 1 and 2, Table II), the extraordinarily fast addition of V to VI (run 3, Table II) eliminates the possibility of V combining with I to form VII, a product which it is practically impossible to separate from III.

Experimental

Isobutyrylacetonitrile.—In a 1-liter, 3-necked flask fitted with a dropping funnel, reflux condenser and vacuum seal stirrer were placed 46 g. (2 atoms) of powdered sodium (powdered under xylene and washed twice with anhydrous ether) and 350 cc. of anhydrous ether. During the course of two to three hours 92 g. (2 moles) of absolute alcohol was slowly added from the dropping funnel. The mixture was stirred, without heating until the reaction ceased and the ether then removed by distillation. To the remaining sodium ethoxide was added a mixture of 77.3 g. (0.67 mole) of ethyl isobutyrate and 27.3 g. (0.67 mole) of acetonitrile. The mixture was heated with stirring for three hours at 115–120° whereupon the alcohol formed in the reaction was distilled off under slightly reduced pressure. Another portion of 0.67 mole of each of the reactants was added, the mixture refluxed for an additional three hours and the alcohol removed as before. This process was repeated until a total of 2 moles each of ethyl isobutyrate and acetonitrile had been added. The mixture was then cooled, decomposed with ice water containing a slight excess of acetic acid, extracted with ether, washed with 5% sodium bicarbonate and water and finally dried over anhydrous sodium sulfate. The ether was then removed and the product distilled under diminished pressure. A light straw-colored oil, b. p. 102–104 (12–13 mm.), came over; yield 98 g. (44%).

Anal. Calcd. for C_6H_9ON: N, 12.61. Found: N, 12.70.

When allowed to stand for several weeks isobutyrylacetonitrile gradually darkened and a sample left standing for several months polymerized to a light brown gelatinous mass.

Ethyl Isobutyrylacetate (II).—A solution of 222 g. (2 moles) of isobutyrylacetonitrile in 92 g. (2 moles) of absolute alcohol was cooled in an ice-salt bath and dry hydrogen chloride passed in until 71 g. (2 moles) had been absorbed. Upon standing in the ice-bath overnight the mixture set to a mass of crystals of the imino ester hydrochloride. This product was washed with ether to remove unchanged nitrile and hydrolyzed by dissolving in water and allowing to stand at room temperature for several hours. The resultant ester layer was taken up in ether, dried over anhydrous sodium sulfate and, after removal of the ether, distilled. The yield was 251 g. (81%), b. p. 90–92° (15–16 mm.), n_D^{25} 1.4245, d_4^{25} 0.9854. This keto ester has been prepared previously by the partial hydrolysis of isobutyrylacetoacetic ester.[2]

Benzalmalonic Ester (I).—In a 3-liter flask were placed 212 g. (2 moles) of benzaldehyde (freshly distilled) and 320 g. (2 moles) of diethyl malonate. This mixture was cooled to −5–0° and 10 cc. of piperidine added. The reaction mixture then was allowed to come to room temperature and to stand with occasional shaking for about thirty-six hours. After this time the reaction product was fractionated under diminished pressure. The first fraction consisted of piperidine and water; the second fraction was a mixture of benzaldehyde and malonic ester. Finally, the benzalmalonic ester fraction, b. p. 160–163° (7 mm.), distilled.[3] The yield was 375–425 g. (74–86%).

(2) Bouveault, *Compt. rend.*, **131**, 45 (1900).
(3) Knoevenagel, *Ber.*, **31**, 2591 (1898).

Ethyl α-Isobutyrylcinnamate (VI).—In a 1-liter flask was placed a mixture of 159 g. (1.5 moles) of freshly distilled benzaldehyde and 237 g. (1.5 moles) of ethyl isobutyrylacetate (II). The reaction mixture was mixed thoroughly and cooled to −5° with ice–salt and 8 cc. of piperidine added. The mixture was shaken, left standing in the ice-bath for a few hours and then allowed to stand at room temperature with occasional shaking for forty-eight hours. Upon distillation under diminished pressure there was obtained 316 g. (86%) of ethyl α-isobutyrylcinnamate; b. p. 148–153 (3 mm.); n_D^{25} 1.5384, d_4^{25} 1.0543.

Anal. Calcd. for $C_{15}H_{18}O_3$: C, 73.13; H, 7.37. Found: C, 73.15; H, 7.30.

Ethyl α-Carbethoxy-α′-isobutyryl-β-phenylglutarate (III) from Benzalmalonic Ester (I) and Isobutyrylacetic Ester (II).—In a 500 cc., 3-necked flask, fitted with a separatory funnel, reflux condenser and copper blade stirrer, were placed 55.3 g. (0.35 mole) of II, 125 cc. of anhydrous ether, 7 cc. of absolute alcohol and 0.7 g. (0.035 gram atom) of sodium. When the sodium had all dissolved 87 g. (0.35 mole) of I was added to the reaction mixture and the separatory funnel washed out with an additional 75 cc. of ether. Heat was liberated upon addition of I to the ether solution. The mixture was stirred under gentle refluxing for the time indicated in Table I and then the reaction was stopped by the addition of ice water containing a slight excess of acetic acid. The ether solution was washed once with 5% sodium bicarbonate solution, once with water and finally dried over anhydrous sodium sulfate. After removal of the ether the reaction products were fractionally distilled through a 30-cm. Widmer column. The following fractions were collected and weighed: 85–90° (15 mm.) (II and V); 148–152° (3 mm.) (I and VI); 186–193° (3 mm.) (III). The determination of the amount of ethyl isobutyrylacetate (II) in the first fraction is based on the fact that this ester is saponified quantitatively by 1 *N* sodium hydroxide into sodium carbonate and the corresponding ketone whereas malonic ester is converted into sodium malonate by this reagent. Approximately 2 g. of the mixture of II and V was weighed out accurately into a Pyrex bomb tube, 50 cc. of 1 *N* sodium hydroxide added and the tube sealed and heated at 130° for eight hours to ensure complete saponification. The tube was then cooled, opened and the amount of sodium carbonate determined by acidifying with 50% sulfuric acid, bubbling carbon dioxide-free air through the mixture for one hour at room temperature. After passing through concentrated sulfuric acid and dehydrite the evolved carbon dioxide was absorbed in ascarite and weighed. Check runs on known mixtures of malonic and isobutyrylacetic esters and on pure samples of each showed this method of estimation to be accurate to within 3%.

The results obtained in these experiments are shown in Table I.

Preparation of III from Malonic Ester (V) and Ethyl α-Isobutyrylcinnamate (VI).—This reaction was carried out in the same manner as described above except that 0.35 mole each of V and VI were used instead of I and II. The results are shown in Table II.

Pure ethyl α-carbethoxy-α′-isobutyryl-β-phenylglutarate boils at 188–190° (3 mm.), n_D^{25} 1.4929, d_4^{25} 1.1198.

Anal. Calcd. for $C_{22}H_{30}O_7$: C, 64.99; H, 7.47. Found: C, 65.34; H, 7.47.

Summary

Ethyl α-carbethoxy-α′-isobutyryl-β-phenylglutarate has been prepared by the addition of ethyl isobutyrylacetate to benzalmalonic ester and also by the addition of malonic ester to ethyl α-isobutyryl cinnamate. Some data on the relative rate and retrogression of the Michael reaction are presented and discussed.

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The Acetoacetic Ester Condensation. VI. A Study of the Mechanism of the Reaction

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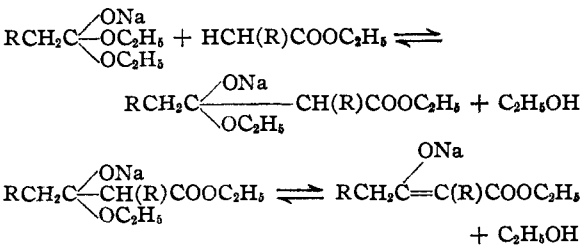
In a previous paper[1] it was pointed out that Dieckmann's interpretation of the acetoacetic ester condensation as a two-phase reversible reaction



failed to explain the significant fact that an ester, such as ethyl isobutyrate, having only one hydrogen on the α-carbon atom, does not undergo the first phase of the reaction even when conditions are such as to allow for the removal of the alcohol as it is formed in the reaction mixture.

Nevertheless, certain types of esters have been reported to undergo an internal acetoacetic ester condensation in which an α-carbon atom possessing only one hydrogen atom is involved. Perkin and Thorpe[2] have reported the condensation of 1,1 - dimethyl - 2,3 - dicarbethoxy - 3 - diethyl-

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

(2) Perkin and Thorpe, *J. Chem. Soc.*, **79**, 736 (1901); *cf.* also Ingold and Thorpe, *ibid.*, **115**, 330 (1919); Farmer and Ingold, *ibid.*, **117**, 1362 (1920).