tages over methods which have been used previously for the isolation of this substance. This work and earlier work with vitamin B_1 indicate that such procedures are useful in the fractionation of certain members of the "B complex."

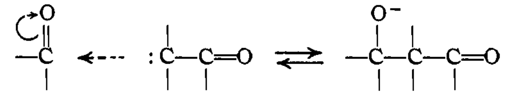
NEW BRUNSWICK, N. J. RECEIVED JULY 19, 1937

[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, DUKE UNIVERSITY]

Certain Condensations Brought about by Bases. I. The Condensation of Ethyl Isobutyrate to Ethyl Isobutyryl-isobutyrate[1]

BY CHARLES R. HAUSER AND W. B. RENFROW, JR.

In this Laboratory a study has been made recently of certain organic elimination reactions which are brought about by bases.[2] The view has been held that these reactions are initiated or facilitated by the removal of a proton from the organic compound. This view has been applied also to certain condensations that are brought about by bases, and which may be regarded as "aldol types," such as the Claisen,[3] Perkin,[4] etc. These condensations are considered to proceed through the intermediate formation of enolates.[5] In the presence of the base a proton is removed from the group $\mathrm{H{-}\overset{|}{\underset{|}{C}}{-}\underset{|}{C}{=}O}$ to form a negative enolate ion, which may be represented in two resonance forms,[6] (a) $\mathrm{:\overset{|}{\underset{|}{C}}:\underset{|}{C}::\underset{\cdot\cdot}{O}:}$ and (b) $\mathrm{\overset{|}{\underset{|}{C}}::\underset{|}{C}:\overset{\cdot\cdot}{\underset{\cdot\cdot}{O}}:}$. The condensation may perhaps be represented most simply as the reaction of (a) with the carbonyl group of a molecule which has not been converted into an enolate. The free pair of electrons of (a) are accepted and shared by the potentially positive carbon atom of the carbonyl group,[7] and the negative charge shifts to oxygen, thus

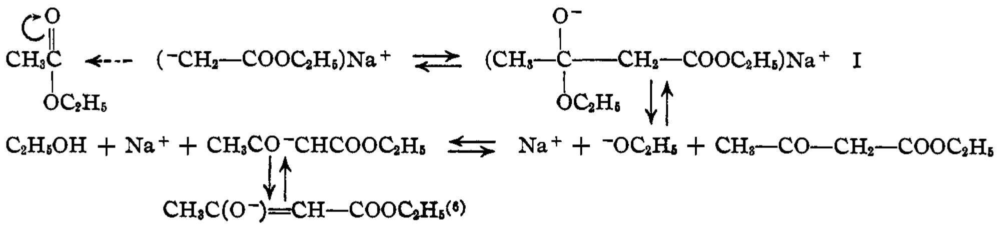


$$\mathrm{\underset{|}{\overset{\curvearrowright O}{\overset{\|}{-C}}}\ \dashleftarrow\ :\overset{|}{\underset{|}{C}}{-}\underset{|}{C}{=}O\ \rightleftharpoons\ -\underset{|}{\overset{O^-}{\overset{|}{C}}}{-}\underset{|}{\overset{|}{C}}{-}\underset{|}{C}{=}O}$$

The condensation does not usually proceed to completion, however, unless a further reaction occurs. In the Perkin, the elimination of water allows the process to be completed, and in the Claisen condensation of an ester, the release of ethylate ion and the formation of an enolate of the condensation product appears to furnish the necessary condition for allowing the reaction to go to completion.

The Claisen condensation of ethyl acetate in the presence of sodium ethylate may be represented as a series of equilibria.

$$\mathrm{CH_3COOC_2H_5 + C_2H_5O^-Na^+ \rightleftharpoons {}^-CH_2{-}COOC_2H_5 + Na^+ + C_2H_5OH}$$
$$\downarrow\uparrow$$
$$\mathrm{CH_2{=}C(O^-){-}OC_2H_5}^{(6)}$$



$$\mathrm{CH_3\underset{OC_2H_5}{\overset{\curvearrowright O}{C}}\ \dashleftarrow\ ({}^-CH_2{-}COOC_2H_5)Na^+ \rightleftharpoons (CH_3{-}\underset{OC_2H_5}{\overset{O^-}{C}}{-}CH_2{-}COOC_2H_5)Na^+\quad I}$$
$$\downarrow\uparrow$$
$$\mathrm{C_2H_5OH + Na^+ + CH_3CO^-CHCOOC_2H_5 \leftrightarrows Na^+ + {}^-OC_2H_5 + CH_3{-}CO{-}CH_2{-}COOC_2H_5}$$
$$\downarrow\uparrow$$
$$\mathrm{CH_3C(O^-){=}CH{-}COOC_2H_5}^{(6)}$$

The negative enolate ion of ethyl acetate formed in the first step condenses with the carbonyl group of a molecule of the ester to form the negative ion of (I). This negative ion releases ethylate ion, which immediately removes a proton from the

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[1] This paper embodies a part of the material presented by W. B. Renfrow, Jr., to the Graduate School of Duke University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

[2] Hauser, LeMaistre and Rainsford, THIS JOURNAL, **57**, 1056 (1935); Hauser and Renfrow, *ibid.*, **59**, 121 (1937).

[3] See Cox, Kroeker and McElvain, *ibid.*, **56**, 1173 (1934).

[4] See Arndt and Eistert, *Ber.*, **69**, 2386 (1936).

[5] Various investigators have assumed that these condensations involve the intermediate formation of enolates. See especially (a) Scheibler and Voss, *ibid.*, **53**, 388 (1920); Scheibler, *ibid.*, **59**, 1022 (1926); (b) Chelintzev, *Compt. rend. acad. sci. U. S. S. R.*, **1**, 393 (1935); Chelintzev and Osetrova, *Ber.*, **69B**, 374 (1936); (c) Arndt and Eistert, *ibid.*, **69**, 2384 (1936); (d) Kalnin, *Helv. Chim. Acta*, **11**, 977 (1928); *Ber.*, **69B**, 2843 (1936); (e) Müller, Gawlick and Kreutzmann, *Ann.*, **515**, 97 (1934).

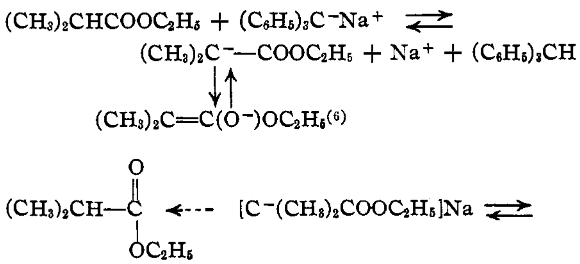
[6] Perhaps the enolate ion is best represented as having a structure intermediate between (a) and (b), formulated as, $(\mathrm{-\underset{|}{\overset{\curvearrowright}{C}}{-}\underset{|}{\overset{\curvearrowright}{C}}{-}O})^{-}$. In this connection see Waters, "Physical Aspects of Organic Chemistry," D. Van Nostrand Co., New York, 1936, p. 314. Also see Sidgwick, *J. Chem. Soc.*, 694, 1937.

[7] In this connection see Waters, "Physical Aspects of Organic Chemistry," pp. 170, 383.

methylene group of the keto ester to give the enolate of the latter. Since ethyl acetate is a weaker acid than ethyl alcohol, the equilibrium of the first step will be on the side of the free ester. But since the acetoacetic ester is a stronger acid than ethyl alcohol, the equilibrium of the last step will be on the side of the sodium enolate. Apparently, acetoacetic ester is a strong enough acid so that, in the presence of sodium ethylate, the series of equilibria is shifted in the direction of its enolate.

A similar mechanism has been proposed recently by Chelintzev,[5b] who, however, did not represent the sodium enolates in the ionic forms. Arndt and Eistert[5c] also have proposed a similar mechanism, but they indicated the direct removal of alcohol from (I), rather than the release of ethylate ion as shown above. In the earlier mechanisms[8] it usually was assumed that sodium ethylate added to the carbonyl group of the ester, followed by the elimination of alcohol from the sodium ethylate addition compound and another molecule of the ester.

The failure of esters of the type $R_2CHCOOC_2H_5$ to undergo the acetoacetic ester condensation in the presence of sodium ethylate is well known.[9] A consideration of the mechanism discussed above leads to the conclusion that esters of this type should condense if treated with a base which is sufficiently strong to form an enolate of the condensation product. The type of enolate that would be formed may be represented by the formula, $R_2C{=}\overset{\overset{O^-Na^+}{|}}{C}{-}CR_2COOC_2H_5$. In agreement with this conclusion we have found that ethyl isobutyrate, when treated with sodium triphenylmethyl, forms isobutyryl-isobutyrate. The reactions may be represented as follows

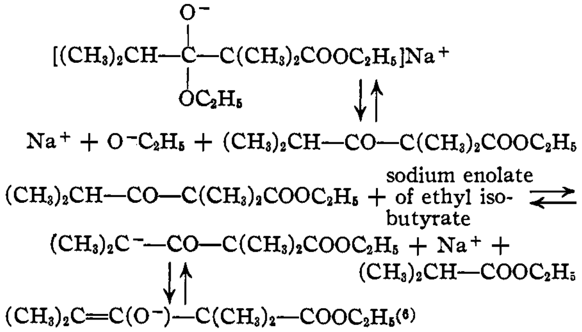


$$(CH_3)_2CHCOOC_2H_5 + (C_6H_5)_3C^-Na^+ \rightleftarrows (CH_3)_2C^-{-}COOC_2H_5 + Na^+ + (C_6H_5)_3CH$$

$$\downarrow\uparrow$$

$$(CH_3)_2C{=}C(O^-)OC_2H_5{}^{(6)}$$

$$(CH_3)_2CH{-}\underset{\underset{OC_2H_5}{|}}{\overset{\overset{O}{\|}}{C}} \dashleftarrow [C^-(CH_3)_2COOC_2H_5]Na \rightleftarrows$$



$$[(CH_3)_2CH{-}\underset{\underset{OC_2H_5}{|}}{\overset{\overset{O^-}{|}}{C}}{-}C(CH_3)_2COOC_2H_5]Na^+$$

$$\downarrow\uparrow$$

$$Na^+ + O^-C_2H_5 + (CH_3)_2CH{-}CO{-}C(CH_3)_2COOC_2H_5$$

$$(CH_3)_2CH{-}CO{-}C(CH_3)_2COOC_2H_5 + \begin{array}{c}\text{sodium enolate}\\ \text{of ethyl iso-}\\ \text{butyrate}\end{array} \rightleftarrows$$

$$(CH_3)_2C^-{-}CO{-}C(CH_3)_2COOC_2H_5 + Na^+ + (CH_3)_2CH{-}COOC_2H_5$$

$$\downarrow\uparrow$$

$$(CH_3)_2C{=}C(O^-){-}C(CH_3)_2{-}COOC_2H_5{}^{(6)}$$

The first step is presumably the formation of the sodium enolate of ethyl isobutyrate and triphenylmethane. Although the enolate has not been isolated,[10] its presence is indicated by the fact that with benzoyl chloride ethyl benzoyldimethylacetate is formed.[11] In a similar manner we have condensed the enolate of ethyl isobutyrate with isobutyryl chloride to form ethyl isobutyryl-isobutyrate.

The condensation of ethyl isobutyrate has been carried out by treating the ester with approximately one-half of the molecular equivalent of sodium triphenylmethyl. The red color of the latter disappeared after several minutes. Since the reaction of sodium triphenylmethyl with ethyl isobutyrate appears to go practically to completion, the enolization of ethyl isobutyrylisobutyrate (last step), apparently is brought about by the action of the enolate of ethyl isobutyrate as shown above.[12] The fact that a considerable amount of unchanged ethyl isobutyrate is recovered is in agreement with this view. It has been found also that when the condensation is carried out using only a small excess of the ethyl isobutyrate, the yield of condensation product is approximately the same.

The condensation product has been identified as ethyl isobutyryl-isobutyrate[13] by its boiling point and by ketonic hydrolysis. When the condensation product was heated with dilute alkali, diisopropyl ketone was obtained. This was identified by its boiling point and by converting it into the semicarbazone. The latter was analyzed and shown to be identical with the

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(8) For example, see Claisen, *Ber.*, **20**, 651 (1887); Dieckmann, *ibid.*, **33**, 2670 (1900). Also, see *J. Chem. Soc.*, *Ann. Reports*, 200 (1934).

(9) In this connection see especially, (a) McElvain, THIS JOURNAL, **51** 3127 (1929); (b) *J. Chem. Soc.*, *Ann. Reports*, 203 (1934).

(10) Schlenk, Hillemann and Rodloff [*Ann.*, 487, 135 (1931)] have isolated and analyzed the enolate of methyl diphenylacetate, and have shown that it condenses with acid chlorides.

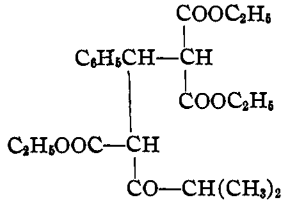
(11) Scheibler and Stein, *J. prakt. Chem.*, **139**, 105 (1934); also see ref. 5e.

(12) In general, ketones are more readily enolizable than esters of similar constitution. See Conant, "The Chemistry of Organic Compounds," The Macmillan Co., New York, 1933, p. 233.

(13) This compound has been prepared previously from ethyl α-bromoisobutyrate and magnesium: Salkind, *Chem. Centr.*, **77**, II, 315 (1906); Zeltner, *Ber.*, **41**, 592 (1908).

semicarbazone prepared from a sample of diisopropyl ketone which was synthesized from isopropylmagnesium bromide and isobutyronitrile.

It has been generally considered that in order for an acetoacetic ester type of condensation to occur with simple esters there must be at least two hydrogen atoms on the alpha carbon atom of the ester.[14] The results presented in this paper, however, show that condensation of this type may occur when there is only one hydrogen on the alpha carbon atom, provided that the base used is sufficiently strong to enolize the hydrogen on the gamma carbon atom of the condensation product. Recently, Cox, Kroeker and McElvain[3] have shown that even sodium ethylate, which is not sufficiently strong as a base to condense ethyl isobutyrate,[15] is capable of effecting an internal condensation with compounds of type II,


$C_6H_5CH[CH(COOC_2H_5)_2]CH(COOC_2H_5)CO{-}CH(CH_3)_2$ II

in which there is only one active hydrogen on any single carbon atom. There are available in these compounds, however, two active hydrogens attached to different carbon atoms, and condensation takes place in such a way that the enolate of the condensation product can be formed in the presence of sodium ethylate.

Experimental

Preparation of Sodium Triphenylmethyl.—Sodium triphenylmethyl was prepared by a modification of the method of Schlenk and Ochs.[16]

A solution of 63 g. (0.226 mole) of triphenylchloromethane in 1500 cc. of dry ether was prepared in a reagent bottle of approximately 2-liter capacity and the air in the bottle replaced by dry nitrogen. To this was added 2100 g. of 1% sodium amalgam and the bottle stoppered by a tightly fitting ground-glass stopper which had been greased with a little Lubriseal. The bottle was clamped in a mechanical shaker and shaken vigorously. A persistent blood-red color developed after about fifteen minutes. After shaking for three hours, the bottle was removed from the shaker and allowed to stand until the sodium chloride had settled to the bottom. The ether solution of sodium triphenylmethyl was removed from the sodium chloride and amalgam by the following procedure. The glass stopper of the reagent bottle was removed and replaced immediately by a closely-fitting two-holed cork stopper carrying one glass tube that extended about a centimeter below the bottom of the cork, and another glass tube that reached to within about 4 cm. of the bottom of the reagent bottle. The short tube was attached through a drying train to a nitrogen tank. The long tube was bent in a U-shape with the end just below the bottom of a cork stopper that was fitted tightly into the top of a nitrogen-filled 2-liter Erlenmeyer flask. The stopper in the Erlenmeyer flask also contained a short-stem separatory funnel. The cork stoppers were sealed over with paraffin. The stopcock of the separatory funnel was opened slightly and the ether solution of sodium triphenylmethyl forced over into the nitrogen-filled Erlenmeyer flask by means of nitrogen from the tank. By proper adjustment of the height of the glass tube above the bottom of the reagent bottle it was possible to remove practically all of the ether solution of sodium triphenylmethyl from the sodium chloride and amalgam.

Condensation of Ethyl Isobutyrate.—Ethyl isobutyrate purchased from the Eastman Kodak Company was washed thoroughly with 10% sodium carbonate solution, dried over Drierite for several days and fractionally distilled. The portion boiling at 110–111° was used for the condensation experiments.

The solution of sodium triphenylmethyl prepared as described above was shaken gently while 53 cc. (0.4 mole) of ethyl isobutyrate was added slowly through the separatory funnel. The color changed from deep red to light orange within five minutes after the ester had been added. After standing for twelve hours at room temperature the light orange color still persisted and a white flocculent precipitate was present. The reaction mixture was then distilled on a water-bath until the volume had been reduced to 300–400 cc. The mixture was cooled in an ice-bath and 20 cc. of glacial acetic acid added rapidly. A voluminous white precipitate formed immediately. Cold water was added until two homogeneous solutions were obtained. The layers were separated, and the organic layer washed with sodium carbonate solution until it reacted basic to litmus paper. The organic layer was separated from the carbonate solution, dried over Drierite, and as much material as possible distilled from a boiling water-bath. The liquid which failed to distil on the water-bath was transferred to a 250-cc. Claisen flask and distilled at 18 mm. All material boiling up to 180° was distilled from the triphenylmethane which remained as a residue in the distilling flask. The distillate was placed in a 125-cc. Claisen flask and again distilled at 18 mm. All material boiling up to 110° was collected. The distillate was transferred to a 50-cc. flask fitted with a fractionating column and 14 cc. of ethyl isobutyrate boiling at 110–111° under atmospheric pressure was distilled over. The liquid remaining after the ethyl isobutyrate had been distilled off was transferred to a 50-cc. Claisen flask and distilled at 18 mm. Practically all of the material distilled at 95–96°. This material was transferred to a

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(14) See, for example, ref. 4.

(15) McElvain[9a] was unable to force the condensation of ethyl isobutyrate in the presence of sodium ethylate, even when conditions were arranged so that any alcohol formed would be continually removed by distillation. This result might have been anticipated on the basis of the theory presented in this paper, because sodium ethylate is not capable of forming an appreciable amount of the enolate of ethyl isobutyryl-isobutyrate.

(16) Schlenk and Ochs, *Ber.*, **49**, 608 (1916).

25-cc. distilling flask and distilled at atmospheric pressure. A yield of 9.45 g. of ethyl isobutyryl-isobutyrate boiling at 201–202° (corr.) was obtained. This is a yield of 35% of the theoretical amount based on the quantity of ethyl isobutyrate used minus that recovered, and a yield of 45%, based on the amount of triphenylchloromethane used. This compound, synthesized in another way,[13] has been reported to boil at 199–201° and at 202.5–203°.

The condensation was also carried out[17] using the same amount of sodium triphenylmethyl with 37 cc. (0.276 mole) of ethyl isobutyrate, in which the molecular ratio of the former to the latter is about one to one and one-fifth. After standing for about four days the reaction mixture was treated with acetic acid, water and carbonate solution as described above. After the ether had been evaporated on a water-bath the solution was chilled in an ice-bath, and the triphenylmethane which precipitated filtered off and washed with cold ether. The condensation product was purified by two vacuum distillations and by one distillation at atmospheric pressure. The yield was 30% of the theoretical amount based on the ethyl isobutyrate used.

The condensation product (5.6 g.) was refluxed for five hours with a solution of 4 g. of potassium hydroxide in 50 cc. of water. A further 3 g. of potassium hydroxide was added and the solution refluxed for five hours more, after which the two layers were separated. The organic layer was dried and distilled through a fractionating column. A yield of 3.7 cc. of diisopropyl ketone boiling at 123–124°[18] was obtained. The semicarbazone of this ketone melted at 160° (corr.) after three crystallizations from alcohol–water mixtures. A mixed melting point of this semicarbazone with a sample of the semicarbazone of diisopropyl ketone which had been prepared from isopropylmagnesium bromide and isobutyronitrile was also found to be 160° (corr.). The melting point previously reported[18] for this semicarbazone was 151–152°.

Reaction of Enolate of Ethyl Isobutyrate with Isobutyryl Chloride.—To an ice-cold solution of sodium triphenylmethyl prepared from 12 g. (0.043 mole) of triphenylchloromethane, 350 cc. of ether and 400 g. of 1% sodium amalgam was added a solution of 5.8 cc. (0.043 mole) of ethyl isobutyrate in 15 cc. of ether. The solution was shaken for five to ten minutes in the ice-bath, during which time the red color of sodium triphenylmethyl was replaced by a light orange color. No appreciable amount of precipitate formed, but the solution became somewhat cloudy. To the ether solution of the enolate was added 4.5 g. (0.0425 mole) of isobutyryl chloride in 10 cc. of ether. A considerable quantity of a flocculent white precipitate came down at once. After standing overnight most of the ether was removed from the mixture by heating it on a boiling water-bath. The residue was cooled in an ice-bath and treated with 7 cc. of glacial acetic acid. The resulting precipitate of sodium acetate was dissolved in cold water and the layers separated. The organic layer was washed with sodium carbonate solution and dried over Drierite. The solution was then distilled at atmospheric pressure and all material boiling up to 250° was collected. A residue of triphenylmethane remained in the distilling flask. The distillate was again distilled and all material boiling up to 210° was collected. By careful distillation of this material 3.2 g. of ethyl isobutyryl-isobutyrate boiling at 196–202° under atmospheric pressure was obtained. This product was identified by hydrolysis to diisopropyl ketone. The semicarbazone of the latter melted at 159–160°.

Synthesis of Diisopropyl Ketone from Isobutyronitrile and Isopropylmagnesium Bromide.—Isopropylmagnesium bromide was prepared by slowly adding a solution of 50 g. of isopropyl bromide in 75 cc. of dry ether to 10 g. of magnesium in 50 cc. of ether according to the usual procedure for preparation of a Grignard reagent. To this solution was added 18.5 g. of isobutyronitrile[19] and the mixture allowed to stand overnight at room temperature. A white crystalline precipitate formed. The ether solution and precipitate were transferred cautiously into a 1-liter round-bottomed flask containing 150 cc. of approximately 10 *N* sulfuric acid and crushed ice. The material was then distilled with steam. The distillate was extracted with ether, and the extract dried with Drierite. The ether was removed and the ketone distilled. A yield of 17.1 g. of diisopropyl ketone boiling at 123–125° was obtained. A portion of this material boiling at 124° gave a semicarbazone that melted at 160° (corr.) after one crystallization from an alcohol–water mixture. The melting point was not changed by three additional crystallizations from alcohol–water mixtures.

A micro-analysis of the semicarbazone for nitrogen by the Dumas method was carried out by the Arlington Laboratories, Arlington, Virginia. Calcd. for $C_8H_{17}ON_3$: N, 24.54. Found: N, 24.31, 24.36.

Summary

1. It has been shown that ethyl isobutyrate when treated with sodium triphenylmethyl condenses to form ethyl isobutyryl-isobutyrate. This is regarded as an acetoacetic ester type of condensation.

2. A mechanism for the acetoacetic ester condensation is discussed.

DURHAM, N. C. RECEIVED JULY 12, 1937

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[17] This experiment was carried out by R. H. Dick in this Laboratory.

[18] This is the boiling point recently reported for this ketone [Bruzau, *Ann. Chim.*, (11) **1**, 267 (1934)].

[19] This compound was prepared by distilling isobutyramide with phosphorus pentoxide.