[Contribution from the Chemistry Department of Duke University]

Condensations Brought about by Bases. IV. The Condensation of Ethyl Isobutyrate with Benzoyl Chloride, Benzoic Anhydride and Phenyl Benzoate as Examples of the Claisen Type of Condensation[1]

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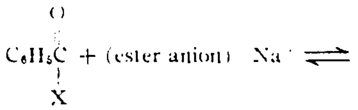
The general course of the Claisen type of condensation has been outlined in the third paper of this series.[2] It was pointed out that any reaction involving the condensation of a metallic enolate with a compound of the type RCOX, where X is an atom or group that is removed as an anion, may be classified as a Claisen type of condensation.

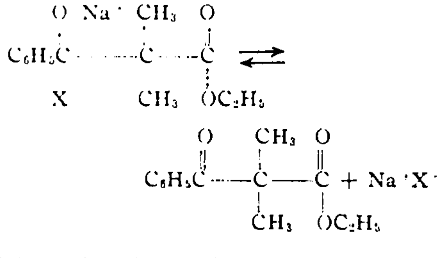
The purpose of this paper has been to investigate the possibility of condensing the simple esters, ethyl acetate, ethyl propionate and ethyl isobutyrate, with a series of compounds of the type C_6H_5COX, using sodium triphenylmethyl as the base. In order to minimize the competing reaction of sodium triphenylmethyl with RCOX, it seemed expedient first to convert the ester into its enolate by means of the sodium triphenylmethyl and then allow the enolate to condense with RCOX, but this procedure has been satisfactory only with ethyl isobutyrate.

Ethyl isobutyrate was added to an ether solution of sodium triphenylmethyl, and, after eight to ten minutes, benzoyl chloride,[3] benzoic anhydride, or phenyl benzoate was added. These reactions gave good yields (50–55%) of the carbon carbon condensation product, ethyl benzoyldimethylacetate. No oxygen derivative was isolated. These carbon–carbon condensations, as well as the one between ethyl isobutyrate and ethyl benzoate,[1] are regarded as examples of the Claisen type of condensation. They may be represented by the following equations, where X of component A is chlorine, benzoate, phenoxide or ethoxide.

$$(CH_3)_2CHCOOC_2H_5 + (C_6H_5)_3C\ Na^+ \rightleftharpoons \text{(ester anion)}^-\ Na^+ + (C_6H_5)_3CH$$



$$C_6H_5\overset{\overset{O}{\|}}{\underset{\underset{X}{|}}{C}} + \text{(ester anion)}^-\ Na^+ \rightleftharpoons$$



$$C_6H_5\overset{\overset{O^-\ Na^+}{\vdots}}{\underset{\underset{X}{\vdots}}{C}}\cdots\overset{\overset{CH_3}{\vdots}}{\underset{\underset{CH_3}{}}{C}}\cdots\overset{\overset{O}{|}}{\underset{\underset{OC_2H_5}{\vdots}}{C}} \rightleftharpoons C_6H_5\overset{\overset{O}{\|}}{C}-\overset{\overset{CH_3}{|}}{\underset{\underset{CH_3}{|}}{C}}-\overset{\overset{O}{\|}}{\underset{\underset{OC_2H_5}{|}}{C}} + Na^+X^-$$

It should be pointed out that in order to obtain ethyl benzoyldimethylacetate when X is ethoxide it is necessary to acidify the reaction mixture within a short time,[5] because on standing in the presence of ethoxide ion (which is formed in the condensation), this β-keto ester is converted into ethyl benzoate and ethyl isobutyrylisobutyrate.[6]

The condensation of ethyl acetate or ethyl propionate with compounds of the type RCOX is difficult to control, first because these esters, in the presence of sodium triphenylmethyl, undergo self condensation very rapidly,[7] and, second, because the β-keto esters which result also are capable of condensing with many compounds of the type RCOX. When ethyl acetate or ethyl propionate is added to an ether solution of sodium triphenylmethyl the deep-red color of the latter changes quickly to a lighter color (orange or yellow) even at 0°; and at room temperature a good yield (43%) of ethyl acetoacetate[8] is obtained from ethyl acetate when the reaction is stopped by acidification within three minutes.[7]

It has not been possible to isolate a good yield of the primary condensation product from the reaction of ethyl acetate or propionate with a compound of the type RCOX. The addition of

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(1) This work was supported in part by a grant from the Duke University Research Council.

(2) Hauser, This Journal, **60**, 1957 (1938).

(3) This reaction serves as perhaps the best method for the preparation of ethyl benzoyldimethylacetate. Previously, it has been carried out on a small scale by Scheibler and Stein, *J. prakt. Chem.*, **139**, 105 (1934).

(4) Renfrow and Hauser, This Journal, **60**, 463 (1938).

(5) Ethyl benzoyldimethylacetate has been obtained from ethyl isobutyrate and ethyl benzoate by stopping the reaction after thirty minutes.[4] The yield of β-keto ester that could be isolated in this case, however, was only about one-third of that obtained from the condensation of ethyl isobutyrate with benzoyl chloride.

(6) Further details of this conversion will be published shortly.

(7) It should be pointed out that ethyl isobutyrate likewise undergoes self-condensation in the presence of sodium triphenylmethyl, but at a slower rate. See Hauser and Renfrow, This Journal, **59**, 1823 (1937).

(8) That the enolate of ethyl acetate is an intermediate in this condensation is indicated by the fact that when the ester is added to sodium triphenylmethyl, followed by the addition of iodine, ethyl iodoacetate is obtained (25% yield). Muller, Gawlick and Kreutzmann, *Ann.*, **515**, 109 (1934).

ethyl propionate to an ether solution of sodium triphenylmethyl at 0°, followed immediately by the addition of benzoyl chloride, gave only high boiling products, which were assumed to be benzoylated β-keto esters. The addition of a mixture of ethyl propionate and phenyl benzoate to sodium triphenylmethyl gave a very small yield of a product which apparently was the primary condensation product, ethyl benzoylmethylacetate, but in this case also a considerable amount of higher boiling material was obtained. Low yields of ethyl benzoylacetate[9] and ethyl benzoylmethylacetate (primary condensation products) have been obtained by adding mixtures of ethyl acetate and ethyl benzoate, and of ethyl propionate and ethyl benzoate, to solutions of sodium triphenylmethyl.

Experimental

Preparation of Sodium Triphenylmethyl.—For the condensations studied in this paper ether solutions of sodium triphenylmethyl were prepared by shaking together 63 g. of triphenylchloromethane, 2100 g. of 1% sodium amalgam and 1500 cc. of dry ether as described previously.[10] In some preparations 1500 g. of 1% sodium amalgam to 63 g. of triphenylchloromethane has been used. It is advisable to stop the shaking with the appearance of the deep-red color, and cool the reaction bottle with a wet towel; the shaking should then be continued for about thirty minutes longer. The ether solution of sodium triphenylmethyl may be analyzed as follows. A 50-cc. aliquot of the solution is run into 25 cc. of water in a separatory funnel. The water is drawn off and the ether solution extracted with three additional 25-cc. portions of water. The water is boiled to expel the ether, cooled and titrated with 0.2 N sulfuric acid using methyl red as indicator. It has been found that when a good grade of triphenylchloromethane is used the yield of sodium triphenylmethyl is almost quantitative.

Results with Ethyl Isobutyrate.—To the solution of sodium triphenylmethyl was added 25 cc. of ethyl isobutyrate, and the mixture shaken and allowed to stand at room temperature for eight to ten minutes. To the solution of enolate was added with shaking a solution of 21.5 cc. of a good grade of benzoyl chloride dissolved in 50 cc. of ether. The mixture became warm and a white precipitate of sodium chloride separated immediately. After standing at room temperature for several hours the mixture was distilled on a water-bath until the volume was reduced to 300–400 cc. A solution of 5 cc. of acetic acid in 300 cc. of water was added and the mixture shaken in a separatory funnel until two homogeneous layers were obtained. The aqueous layer was drawn off, the ether layer shaken with 10% sodium carbonate solution and dried over "Drierite." The ether solution was filtered from the Drierite and distilled on a water-bath until most of the ether was removed. The residue was cooled in a refrigerator and the precipitate of triphenylmethane filtered off and washed with several portions of ether. The filtrate after further removal of ether was distilled at 15 mm. and all material boiling up to 180° collected. The distillate was redistilled at 15 mm., collecting liquid boiling at 120–160°. A final distillation was carried out at 15 mm. and the fraction boiling at 146–148° taken as ethyl benzoyldimethylacetate.[3] The yield was 20.5–22.5 g. (50–55% of the theoretical amount). The isoxazolone prepared as described previously[4] melted at 69–70°.

Anal.[11] Calcd. for $C_{11}H_{11}O_2N$: N, 7.40. Found: N, 7.40, 7.54.

The condensations of ethyl isobutyrate with benzoic anhydride[12] and with phenyl benzoate were carried out in a similar manner. The yield of ethyl benzoyldimethylacetate obtained with benzoic anhydride was approximately the same as when benzoyl chloride was used; the yield obtained with phenyl benzoate was slightly less.

Results with Ethyl Acetate.—To the ether solution of sodium triphenylmethyl was added at room temperature 16 g. of ethyl acetate, and the solution shaken. The color changed in less than a minute from deep red to orange, and further addition of a little ethyl acetate produced no further color change. After standing for three minutes at room temperature 20 cc. of glacial acetic acid was added. The ether solution was washed with dilute sodium carbonate and dried with "Drierite." Most of the ether was distilled from a water-bath through a fractionating column. The remaining solution was cooled and the triphenylmethane which precipitated filtered off. On fractionation a little ethyl acetate was recovered, and 5 g. of ethyl acetoacetate (43% of the theoretical amount) boiling at 73–76° at 14 mm. was obtained.

A mixture of 17 g. of ethyl acetate and 29 g. of ethyl benzoate was added to the ether solution of sodium triphenylmethyl. After standing for several hours the products were isolated in the usual manner. Some ethyl benzoate was recovered and ethyl acetoacetate was obtained. A small fraction (2.9 g.) of ethyl benzoylacetate boiling at 164–168° at 15 mm. was obtained. This is the approximate boiling point reported in the literature.[13] The isoxazolone melted at 151–152° (corr.) which is in agreement with the melting point reported in the literature.[14]

Results with Ethyl Propionate.—Similar to ethyl acetate, ethyl propionate quickly changes the color of sodium triphenylmethyl.

Eighteen grams of ethyl propionate was added to a rapidly stirred ether solution of sodium triphenylmethyl at 0°, followed immediately by the addition of 25 g. of benzoyl chloride. No ethyl benzoylmethylacetate could be isolated. Mixed with triphenylmethane high boiling products were obtained which were assumed to be benzoylated products. These were not further investigated, since we were interested in the primary condensation products.

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(9) A better yield of ethyl benzoylacetate has been obtained from ethyl acetate and ethyl benzoate in the presence of sodium ethoxide; Claisen and Lowman, *Ber.*, **20**, 653 (1887).

(10) Hauser and Renfrow, THIS JOURNAL, **59**, 1825 (1937).

(11) Micro-Dumas by R. L. Peck.

(12) This experiment has been carried out by W. B. Renfrow, Jr.

(13) Claisen, *Ann.*, **291**, 71 (1896); see ref. 9.

(14) Moureu and Lazennec, *Compt. rend.*, **144**, 1281 (1907); Uhlenhuth, *Ann.*, **296**, 38 (1897).

A mixture of 17 g. of ethyl propionate and 35 g. of phenyl benzoate was added to the ether solution of sodium triphenylmethyl at room temperature. After standing overnight the products were isolated in the usual manner. Only a little ethyl propionate and phenyl benzoate were recovered. Similar to the experiment with benzoyl chloride, the triphenylmethane was contaminated with high boiling oils. A small fraction (1.5 g.) boiling at 153–156° at 11 mm. which was apparently ethyl benzoylmethyl acetate was isolated.

A mixture of 17 g. of ethyl propionate and 26 g. of ethyl benzoate was added to the ether solution of sodium triphenylmethyl at room temperature. After fifteen minutes the mixture was acidified with acetic acid, and the products isolated in the usual manner. Some ethyl benzoate was recovered, and ethyl propionylmethylacetate was obtained. Four grams of ethyl benzoylmethylacetate boiling at 154–156° at 11 mm. was isolated. Hope and Perkin[15] give 162–163° as the boiling point at 18 mm. The isoxazolone melted at 120.5–121.5° (corr.). Haller and Bauer[16] give 123–124° as the melting point of the isoxazolone after many recrystallizations.

Summary

1. The enolate of ethyl isobutyrate has been condensed with benzoyl chloride, benzoic anhydride, and phenyl benzoate to give good yields of ethyl benzoyldimethylacetate.

2. Ethyl acetate in the presence of sodium triphenylmethyl gives a good yield of ethyl acetoacetate within three minutes.

3. Ethyl acetate and ethyl propionate condense with ethyl benzoate in the presence of sodium triphenylmethyl but only low yields of ethyl benzoylacetate and of ethyl benzoylmethylacetate have been obtained.

4. These reactions are regarded as examples of the Claisen type of condensation.

DURHAM, NORTH CAROLINA RECEIVED JUNE 11, 1938

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[15] Hope and Perkin, *J. chem. Soc.*, **95**, 2045 (1909).

[16] Haller and Bauer, *Ann. chim.*, [10] **1**, 282 (1923).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

The Kinetics of the Hydrolysis of Ethyl Orthoformate in D_2O–H_2O Mixtures

BY FRANK BRESCIA AND VICTOR K. LA MER

Introduction

Recent work[1] on acid catalysis in heavy water has led to the general criterion that an increase in the rate in D_2O, over that in H_2O, is evidence that an equilibrium is maintained in the first stage of the reaction mechanism whereas a decrease in rate would indicate that the rate-determining step is a proton transfer in the first stage. In the case of a specific hydrogen-ion catalyzed reaction, the rate in H_2O–D_2O mixtures should be proportional to the relative concentration of D^+ and H^+, if these are the ionic species involved in the equilibrium. This was found to be the case for sucrose inversion,[2] which has been studied[3] over the range of H_2O–D_2O mixtures. We shall subject this hypothesis to further test by investigating the hydrolysis of ethyl orthoformate. This reaction,[4] which is specifically catalyzed by hydrogen ion, has been investigated carefully in H_2O for secondary salt[5] and solvent medium[6] effects. Recently, Hornel and Butler[7] have reported two measurements in a water of high deuterium content to determine the effect of deuterium substitution upon the dissociation constant of cacodylic acid.

Since the reaction is exceedingly sensitive to the concentration of hydrogen ions, acetic acid–sodium acetate buffers are well adapted for kinetic study. The thermodynamic and conductive properties of acetic acid have been studied carefully for the entire range of H_2O–D_2O mixtures.[8] The hydrolysis is accompanied by a relatively large volume change and therefore can be studied dilatometrically—a desirable characteristic when dilution must be avoided.

The velocity constant for a constant buffer ratio decreases steadily as the deuterium content of the solvent increases. This is contrary to the principle that the rate of a H^+ ion catalyzed reaction should increase. At the same time, however, the dissociation constant of acetic acid decreases 3.3-fold on passing from H_2O to D_2O so that it is possible that the rate when referred to the actual concentration of H^+ or D^+ ions increases.

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[1] Bonhoeffer, *Trans. Faraday Soc.*, **34**, 252 (1938); Wynne-Jones, *ibid.*, **34**, 245 (1938).

[2] La Mer, *Chem. Rev.*, **19**, 363 (1936); Hamill and La Mer, *J. Chem. Phys.*, **4**, 294 (1936).

[3] Moelwyn-Hughes and Bonhoeffer, *Naturwissenschaften*, **22**, 174 (1934); Gross, Suess and Steiner, *ibid.*, **22**, 662 (1934).

[4] Skrabal, *Z. Elektrochem.*, **33**, 322 (1927).

[5] Brönsted and Wynne-Jones, *Trans. Faraday Soc.*, **25**, 59 (1929).

[6] Harned and Samaras, THIS JOURNAL, **54**, 1 (1932).

[7] Hornel and Butler, *J. Chem. Soc.*, 1361 (1936).

[8] Korman and La Mer, THIS JOURNAL, **58**, 1396 (1936); Chittum and La Mer, *ibid.*, **59**, 2425 (1937).