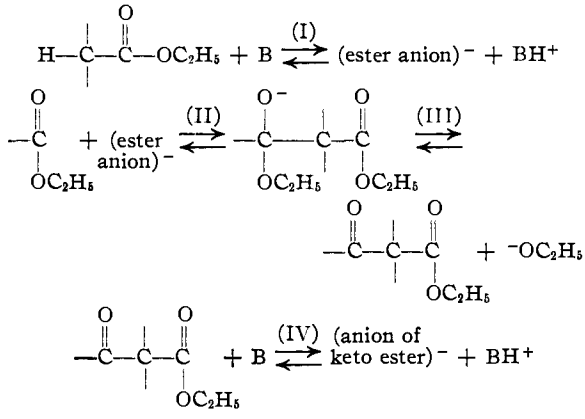
[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

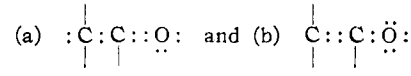
Condensations Brought about by Bases. II. The Condensation of the Enolate of Ethyl Isobutyrate with Ethyl Benzoate and Further Observations on the Claisen Type of Condensation

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

The essentials of the mechanism that has been proposed recently[1] for the acetoacetic ester or Claisen condensation of an ethyl ester in the presence of a base, may be represented by the general equations



The first step consists of an acid–base reaction in which a new acid and a new base are formed. The new base is an ester anion (enolate anion) which may exist in two resonance forms[1]



Step (II) involves the condensation of the ester anion with the carbonyl group of the original ester, or of a different ester.[2] The resonance form (a) may be considered to undergo this reaction. The anion formed in step (II) releases ethylate ion (step III) to form a β-keto ester. Step (IV) is another acid–base reaction in which the β-keto-ester is converted into its enolate anion. This of course requires an enolizable hydrogen on the β-keto ester.

In all known condensations brought about by sodium ethylate the β-keto ester is converted into its enolate anion. The ethylate ion is sufficiently strong as a base to enolize a hydrogen on the α-carbon atom of most β-keto esters,[3] but it is not a strong enough base to enolize appreciably a hydrogen on the γ-carbon atom of a simple β-keto ester. Accordingly, most simple ethyl esters[3] which have at least two hydrogens on their α-carbon atoms undergo the acetoacetic ester condensation in the presence of the ethylate ion, whereas an ester, such as ethyl isobutyrate, which has only one hydrogen on the α-carbon atom, is not condensed in the presence of this base. The condensation product that would be formed from ethyl isobutyrate is ethyl isobutyryl-isobutyrate, $(CH_3)_2CH\text{-}CO\text{-}C(CH_3)_2COOC_2H_5$, which has no hydrogen on the α-carbon atom, but one on the γ-carbon atom. Recently, we have shown that ethyl isobutyrate undergoes the acetoacetic ester type of condensation when treated with sodium triphenylmethyl, the anion of which is a base of sufficient strength to enolize the hydrogen on the γ-carbon atom of the condensation product. Ethyl isobutyrate has been condensed also by Spielman and Schmidt[4] using the Grignard reagent, mesitylmagnesium bromide, as condensing agent.

On the basis of these facts it has been believed generally that in order for an ester to undergo the Claisen type of condensation, the condensation product (β-keto ester) must be converted into its enolate. Although this may be true for condensations brought about by ethylate ion, an experiment is reported in this paper in which two esters are condensed by means of a stronger base, and the β-keto ester formed is not converted into an enolate.

It has been found that, in the presence of sodium triphenylmethyl, ethyl isobutyrate condenses with ethyl benzoate to form ethyl benzoyldimethylacetate, even though this condensation product cannot be converted into an enolate. In this experiment ethyl isobutyrate has been converted into its ester anion (enolate anion) by means of the triphenylmethyl ion in ether, and the ester anion allowed to condense with ethyl benzoate. After half an hour the reaction mixture was acidified, and the β-keto ester isolated. It should be pointed out that in the presence of

(1) Hauser and Renfrow, THIS JOURNAL, **59**, 1823 (1937).

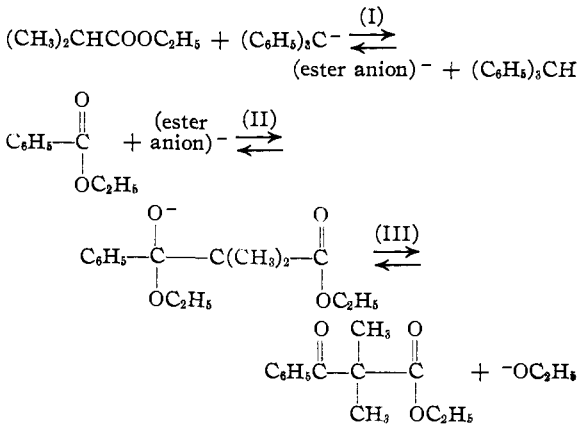
(2) For references to condensations between different esters, see Hickinbottom, "Reactions of Organic Compounds," Longmans Green and Co., New York, 1936, p. 238.

(3) Recently, Roberts and McElvain [THIS JOURNAL, **59**, 2007 (1937)], have shown that neither ethyl isovalerate nor ethyl *t*-butylacetate is condensed by sodium ethylate, although the β-keto ester that would be formed in each case has a hydrogen on the α-carbon atom.

(4) Spielman and Schmidt, *ibid.*, **59**, 2009 (1937).

the reaction mixture, ethyl benzoyldimethylacetate appears to be converted into ethyl benzoate and ethyl isobutyryl-isobutyrate, since these were the only products isolated in an experiment in which the mixture was allowed to stand for several days before acidifying. This phase of the problem is being studied further.

The condensation of ethyl isobutyrate with ethyl benzoate in the presence of sodium triphenylmethyl is considered to follow the course represented above by the general equations, except that step (IV) does not take place. The following equations represent the reactions that probably occur.



It should be pointed out that while the equilibrium of the first step is on the side of the original ester in condensations brought about by sodium ethylate, the corresponding equilibrium in the presence of sodium triphenylmethyl is probably on the side of the ester anion.[1] The greater concentration of ester anion in the latter case favors the condensation. The equilibrium of step (III) is assumed to be on the side of the β-keto ester. It should be noted, however, that any hemi-acetal anion present in the reaction mixture would probably be converted into the β-keto ester when the mixture is acidified.

The available facts on the Claisen type of condensation indicate that a fundamental consideration in these reactions is the change in basicity (and acidity) of the reactants. At the present time only a few preliminary remarks can be made in this connection. In all known condensations of ethyl esters, a weaker base is formed than the one used to initiate the reaction. In the common condensations of ethyl esters by means of the ethylate ion there is a transition from this base to the more weakly basic anion of the β-keto ester. In the condensation reported in this paper there is a transition from the very strong base, triphenylmethyl ion, to the more weakly basic ethylate ion. It should not be concluded, however, that condensation will always occur when it appears to be possible to pass from a stronger to a weaker base, since other factors are probably involved.

Experimental

An ether solution of sodium triphenylmethyl was prepared from 63 g. of triphenylchloromethane, 2100 g. of 1% sodium amalgam, and 1500 cc. of ether in the manner described previously.[1] To this solution was added 23.6 cc. (0.177 mole) of ethyl isobutyrate and, after shaking gently for three minutes, 25.2 cc. (0.177 mole) of ethyl benzoate was added. The solution was allowed to stand with occasional shaking at room temperature for thirty minutes and then poured into a solution of 20 cc. of glacial acetic acid in 75 cc. of ether. The resulting mixture was extracted with water, washed with sodium carbonate solution and dried over "Drierite." After the solution had been concentrated as much as possible from a boiling water-bath, the residue was chilled in an ice box and the resulting precipitate of triphenylmethane filtered off. The filtrate was fractionally distilled and 7.6 g. or 38% of the theoretical amount (calculated from the ethyl benzoate added minus that recovered) of ethyl benzoyldimethylacetate,[5] boiling at 146–148° at 15 mm., was isolated.

Anal.[6] Calcd. for $C_{13}H_{16}O_3$: C, 70.88; H, 7.31. Found: C, 70.57; H, 7.30.

The isoxazolone was prepared by treating 1 g. of the ester with 2 g. of hydroxylamine hydrochloride, and 2 g. of potassium hydroxide in a small amount of water. Sufficient alcohol was added to dissolve the ester (a small amount of potassium chloride precipitated) and the solution allowed to stand overnight. The solution was poured onto crushed ice and the resulting precipitate filtered off and crystallized from ligroin (b. p. 90–120°). The isoxazolone[5] melted at 69–70°, and a mixed melting point with an authentic specimen[7] was also 69–70°. The other major fraction isolated from the filtrate was 12.7 g. of material boiling at 93–98° at 15 mm. This fraction was almost entirely ethyl benzoate, since it gave a 90% yield of benzoic acid when hydrolyzed with dilute alkali.

When the above procedure was varied by allowing the reaction mixture to stand for three days before pouring into acetic acid, no ethyl benzoyldimethylacetate could be isolated, and 22.2 g. of material boiling at 93–98° at 15 mm. was obtained. This material was presumably a mixture of ethyl isobutyryl-isobutyrate and ethyl benzoate. Hydrolysis of this material gave 2.21 g. of diisopropyl

(5) Haller and Bauer [*Ann. chim.*, [10] **1**, 278 (1924)] have reported that ethyl benzoyldimethylacetate boils at 145–146° at 13 mm., and that the corresponding isoxazolone melts at 70–71°.

(6) Micro-analysis by R. L. Peck in this Laboratory.

(7) The sample of isoxazolone used for this purpose had been analyzed. It was prepared from ethyl benzoyldimethylacetate which had been obtained from the enolate of ethyl isobutyrate and benzoyl chloride. The details will be published shortly.

ketone (identified by conversion to the semicarbazone m. p. 159–160°)[1] and 10.4 g. of benzoic acid.

Summary

1. It has been shown that, in the presence of sodium triphenylmethyl, ethyl isobutyrate condenses with ethyl benzoate to form ethyl benzoyldimethylacetate.

2. Further observations are made on the acetoacetic ester or Claisen type of condensation.

DURHAM, N. C. RECEIVED DECEMBER 27, 1937

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Physiologically Active Phenethylamines. I. Hydroxy- and Methoxy-α-methyl-β-Phenethylamines (β-Phenylisopropylamines)

BY E. H. WOODRUFF AND THEODORE W. CONGER[1,2]

The rediscovery of ephedrine by K. K. Chen in 1923 revived interest in the synthesis and pharmacology of β-phenethylamine and related compounds as evidenced by the increased number of publications appearing on the subject since that time.

The fundamental principles regarding the chemical structure necessary for physiological activity, as well as the modifications in structure already investigated, are covered so thoroughly by extensive reviews in the literature[3–5] that any further discussion in connection with the work reported here is not considered necessary. Investigations covered in the reviews mentioned point to the presence of one or more hydroxyl groups in the benzene ring as one of the most potent modifiers of the magnitude of the physiological effects of compounds possessing the basic β-phenethylamine skeleton.

Practically all of the β-hydroxy-(methoxy)-phenethylamines have been prepared[6] and tested pharmacologically.[7]

In spite of the greater recent clinical interest in amines of the β-phenylpropyl series, this series has not been studied so completely. In this work the monohydroxy and methoxy amines of the latter series so far unknown have been prepared for the purpose of pharmacological study. Those previously prepared have been included for the purpose of comparison.

(1) Kalamazoo College Fellow, 1935–1936.

(2) A part of the data is from the thesis of T. W. Conger submitted as partial requirement for the degree of Master of Science from Kalamazoo College, June, 1936.

(3) Chen and Schmidt, *Medicine*, **9**, 1 (1930).

(4) Hartung, *Chem. Rev.*, **9**, 389 (1931).

(5) Council on Pharmacy and Chemistry, *J. A. M. A.*, **109**, 2064 (1937).

(6) Buck, THIS JOURNAL, **54**, 3661 (1932).

(7) Hjort, *J. Pharmacol.*, **52**, 101 (1934).

Experimental

The method used for the preparation of the α-methyl-β-phenethylamines is similar to that used by Buck[6] and Slotta and Heller[8] for the preparation of methoxyphenethylamines and involves the following reactions

$$(CH_3O)C_6H_4CHO \longrightarrow (CH_3O)C_6H_4CH{=}C(CH_3)COOH \longrightarrow (CH_3O)C_6H_4CH_2{-}CH(CH_3)COOH \longrightarrow (CH_3O)C_6H_4CH_2CH(CH_3)CONH_2 \longrightarrow (CH_3O)C_6H_4CH_2CH(CH_3)NH_2 \longrightarrow (HO)C_6H_4CH_2CH(CH_3)NH_2\cdot HCl$$

The older methods for the preparation of α-methylcinnamic acid were found to be inconvenient for the methoxy derivatives so a better method for their synthesis was sought. An excellent preparation for α-alkylcinnamic acids is that recently carried out by Bogert and Davidson[9] who oxidized with hypohalite methyl (α-alkyl styryl) ketones prepared by condensing benzaldehyde with a methyl alkyl ketone in the presence of dry hydrogen chloride gas. With modification this was found to give excellent yields of the methoxy-α-methylcinnamic acids. The other steps in the synthesis follow essentially experimental procedures already appearing in the literature.

Methoxy-α-methylcinnamic Acids.—The hypohalite oxidation of the methyl [(α-methyl) methoxystyryl] ketones to the corresponding cinnamic acid was carried out essentially as described by Bogert and Davidson, as was the preparation of the unsubstituted ketone. When condensing the methoxy aldehydes with methyl ethyl ketone it was necessary to cool the aldehyde–ketone mixture in an ice salt bath during the addition of the hydrogen chloride gas and to allow the reaction to proceed in an electric refrigerator at 0–5° or in the freezing chamber at −10 to −5° for twenty-four to forty-eight hours, instead of at room temperature. It was found further that a practical grade of methyl ethyl ketone could be used. In this case instead of recovering the unused ketone the reaction mixture was taken up in ether, neutralized with solid sodium carbonate and washed thoroughly with water before drying with anhydrous magnesium sulfate and distilling.

(8) Slotta and Heller, *Ber.*, **63**, 3029 (1930).

(9) Bogert and Davidson, THIS JOURNAL, **54**, 334 (1932).