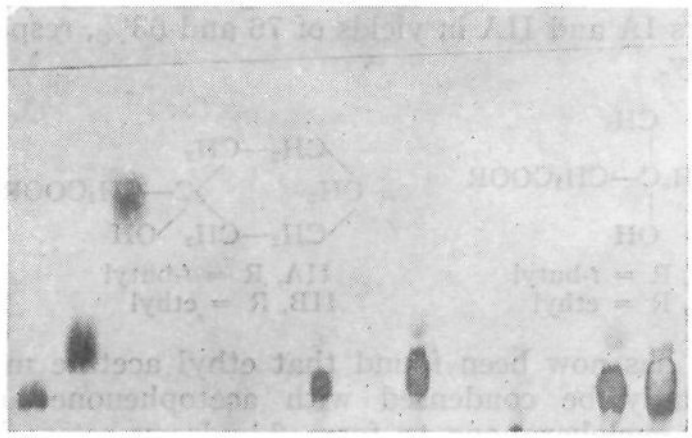
after hydrolysis. The fumarate and malate products however yielded greatly increased ninhydrin reactions after hydrolysis (Fig. 1). The low intensities prior to hydrolysis are explainable on the basis that the conditions employed for synthesis of aspartic acid are identical to those which cause rapid pyrohomopolymerization of aspartic acid to an acid-hydrolyzable product.[2,4] The conversion of malate to aspartate was visibly greater than that of fumarate at 120, 160 and 200°.



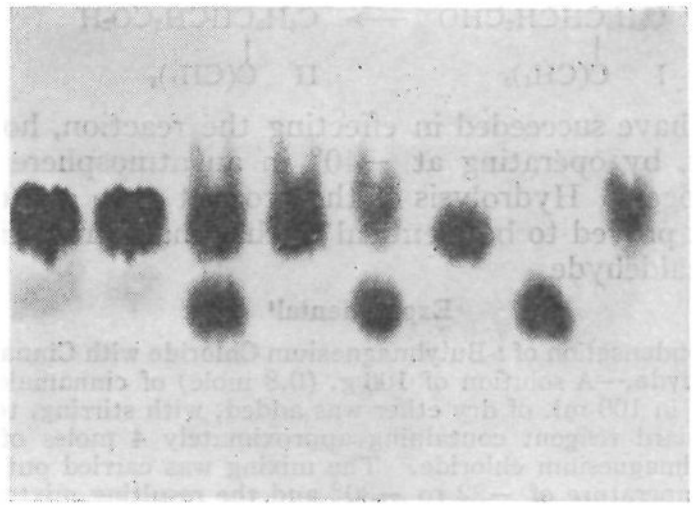
1 2 3 4 5 6 7 8 9 10 11 12 13

Fig. 1.—1, 10 λ of aspartic acid standard; 2, 10 λ of alanine standard; 3, 10 λ of leucine standard, to permit comparisons of R_F; 4, 10 λ of unheated monoammonium fumarate; 5, 10 λ of unheated monoammonium malate; 6, 10 λ of heated monoammonium fumarate; 7, 2 λ of hydrolyzed heated monoammonium fumarate (2 λ); 8, 10 λ of heated monoammonium malate; 9, 1 λ of hydrolyzed heated monoammonium malate showing faint spot with R_F of alanine; 10, 10 λ of hydrolyzed heated monoammonium succinate; 11, 10 λ of hydrolyzed heated ammonium citrate showing non-ninhydrin spot at origin; 12, 10 λ of hydrolyzed heated monoammonium fumarate (this amount shows alanine spot better than does spot 7); 13, same as 12 for monoammonium malate instead of spot 9. Heating was for 3 hours at 200° in tubes of 16 × 150 mm. size in oil-bath. Hydrolyses were performed with concd. hydrochloric acid at 15 lb. steam pressure for 12 hours. The dried products from 1.0 g. of reactant were dissolved in 15.0 ml. of water. Standards were from solutions containing 1.0 mg. of amino acid per ml. Chromatographic solvent was 4 butanol:1 acetic acid:1 water.

In all chromatograms showing additional ninhydrin spots following pyropolymerizations of amino acids and hydrolysis, spots with the R_F of alanine were observed. Inasmuch as the R_F values of α-alanine and of β-alanine, in the butanol–acetic acid solvent used, are the same,[8] new chromatograms were run in pyridine–water (7:3), in which the R_F values differ. The results from the hydrolyzate of heated ammonium malate (Fig. 2) confirm in the second solvent system that the spot is alanine and that this is partly or entirely α-alanine. In this latter system, β-alanine has the same R_F as aspartic acid.

The same conditions can thus yield aspartic acid from a citric cycle acid, can lead to the formation of one or more additional amino acids, and can result in a *proteinoid* polymer from which these amino acids are recovered following hydrolysis. Any concepts of prebiological chemistry must necessarily be highly speculative. If origins of biochemistry are to be considered,[9] however, the experiments reported here indicate that thought must be accorded to a thermal origin of biochemistry. In this connection, it is of interest that, on the basis of taxonomic studies, Copeland[10] suggested the origin of biology in thermal waters.

(8) H. K. Berry, H. E. Sutton, L. Cain and J. S. Berry, Univ. of Texas Publication No. 5109, 1951, p. 22.



1 2 3 4 5 6 7 8

Fig. 2.—1, 10 λ of aspartic acid; 2, 10 λ of α-alanine; 3, 10 λ of β-alanine; 4, 10 λ each of aspartic acid and α-alanine; 5, 10 λ each of aspartic acid and β-alanine; 6, 10 λ each of aspartic acid, α-alanine, and β-alanine; 7, 20 λ of product from ammonium malate heated at 160°; 8, 20 λ of product from ammonium malate heated at 200°. Chromatographic solvent was 7 pyridine:3 water.

(9) S. L. Miller, *Science*, **117**, 528 (1953).
(10) J. J. Copeland, *Ann. N. Y. Acad. Sci.*, **36**, 1 (1936).

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Conjugate Addition of *t*-Butylmagnesium Chloride to Cinnamaldehyde and Ethyl Cinnamate

BY REYNOLD C. FUSON AND LEWIS I. KRIMEN

RECEIVED OCTOBER 15, 1954

The only report of the conjugate addition of a Grignard reagent to an α,β-unsaturated aldehyde was made by Stevens, who succeeded in condensing *t*-butyl- and *t*-amylmagnesium chloride with crotonaldehyde in the 1,4-manner.[1] By the use of the *t*-butyl reagent we have been able to achieve a similar result with cinnamaldehyde. The 1,4-addition product, β-*t*-butylhydrocinnamaldehyde (I), isolated by way of the sodium bisulfite addition compound, underwent oxidation when exposed to the air to give the corresponding acid.

We were able to synthesize β-*t*-butylhydrocinnamic acid (II), which had been described earlier by Koelsch,[2] from ethyl cinnamate and *t*-butylmagnesium chloride. These compounds had been shown by others not to combine in the 1,4-manner under the conditions ordinarily employed for such condensations.[3]

(1) P. G. Stevens, THIS JOURNAL, **57**, 112 (1935).
(2) C. F. Koelsch, *ibid.*, **65**, 1640 (1943).
(3) C. R. Hauser, R. S. Yost and B. I. Ringler, *J. Org. Chem.*, **14**, 26 (1949); A. D. Petrov and P. S. Bataev, *J. Gen. Chem.* (*U.S.S.R.*), **20**, 2236 (1950).

$$\underset{\text{I}}{C_6H_5CHCH_2CHO} \longrightarrow \underset{\text{II}}{C_6H_5CHCH_2CO_2H}$$
$$\quad\quad C(CH_3)_3 \quad\quad\quad\quad C(CH_3)_3$$

We have succeeded in effecting the reaction, however, by operating at −40° in an atmosphere of nitrogen. Hydrolysis of the product gave an acid that proved to be identical to that made from cinnamaldehyde.

Experimental[4]

Condensation of *t*-Butylmagnesium Chloride with Cinnamaldehyde.—A solution of 106 g. (0.8 mole) of cinnamaldehyde in 100 ml. of dry ether was added, with stirring, to a Grignard reagent containing approximately 4 moles of *t*-butylmagnesium chloride. The mixing was carried out at a temperature of −22 to −30° and the resulting mixture, still under nitrogen, was stirred for 18 hours. The product, obtained by treating the mixture with iced hydrochloric acid, was taken up in ether and the ether solution washed with sodium carbonate solution and with water and dried over magnesium sulfate. Evaporation of the solvent under diminished pressure left an amber oil, which was added dropwise, with vigorous stirring, to a warm solution of 51 g. of sodium bisulfite in 459 g. of water. When the addition was complete the mixture was cooled and extracted with two 150-ml. portions of ether. To the aqueous layer, cooled to 0 to 5°, was added, dropwise, a dilute solution of hydrochloric acid. During this addition a small layer of ether was kept in the reaction flask. Stirring was continued for one hour after the addition had been completed and the mixture was then extracted several times with 100-ml. portions of ether. Evaporation of the solvent *in vacuo* left an amber liquid, which was dried in a vacuum desiccator. The infrared spectrum of this oil contains absorption bands to be expected for β-*t*-butylhydrocinnamaldehyde.[5] Attempts to distil the aldehyde brought about decomposition.

Air Oxidation of the Aldehyde.—After prolonged exposure to the air the aldehyde was found to have been oxidized to β-*t*-butylhydrocinnamic acid, a colorless micro-crystalline solid, which was sublimed at 100–106° under a pressure of 0.05–0.01 mm., m.p. 113.5° (cor.). The yield was very low.

Anal.[6] Calcd. for $C_{13}H_{18}O_2$: C, 75.70; H, 8.79. Found: C, 75.55; H, 8.84.

Condensation of *t*-Butylmagnesium Chloride with Ethyl Cinnamate.—A solution of 35.2 g. (0.2 mole) of ethyl cinnamate in 35 ml. of dry ether was added, dropwise with stirring, to a Grignard reagent containing 1 mole of *t*-butylmagnesium chloride previously cooled to a temperature of −40°. The reaction was conducted under an atmosphere of nitrogen. The gray-black reaction mixture, which turned dark brown and finally green, was stirred for 18 hours under nitrogen and decomposed with dilute iced hydrochloric acid. The oil obtained by extraction of the mixture with ether was heated under reflux for 50 hours with a solution of 42 g. of sodium hydroxide in 168 g. of water. The saponification mixture was cooled and extracted with ether, and the aqueous layer was treated with dilute hydrochloric acid. The acidification was conducted in the presence of a layer of ether in order to effect separation of the acid from the silicious material that is precipitated. Evaporation of the ether left the β-*t*-butylhydrocinnamic acid in very low yield. It sublimed at 85–106° under a pressure of 0.05–0.01 mm. to give colorless crystals melting at 90–110°. A second sublimation gave the pure acid, m.p. 113°.

Anal. Calcd. for $C_{13}H_{18}O_2$: C, 75.70; H, 8.79. Found: C, 75.63; H, 8.66.

A mixture of this acid with that obtained from cinnamaldehyde melted at 113.5–114°. Since this work was completed this acid has been made by the addition of *t*-butylmagnesium chloride to cinnamic acid.[7]

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(4) All melting points are corrected.

(5) The infrared spectra mentioned in this paper were recorded and interpreted by Miss Helen Miklas.

(6) The microanalyses were performed by Mr. Joseph Nemeth.

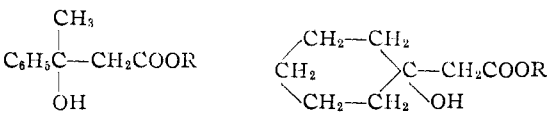
(7) J. H. Wotiz, J. S. Matthews and H. Greenfield, THIS JOURNAL, **75**, 6343 (1953).

Aldol Condensation of Ethyl Acetate with Ketones to Form β-Hydroxy Esters by Lithium Amide[1]

BY CHARLES R. HAUSER AND JACQUE K. LINDSAY

RECEIVED SEPTEMBER 20, 1954

It has recently been shown that the aldol type of condensation between *t*-butyl acetate and ketones or aldehydes to form β-hydroxy esters may be accomplished in good yields with lithium amide.[2] For example, this ester was condensed with acetophenone and with cyclohexanone to give β-hydroxy esters IA and IIA in yields of 76 and 63%, respectively.



IA, R = *t*-butyl
IB, R = ethyl

IIA, R = *t*-butyl
IIB, R = ethyl

It has now been found that ethyl acetate may similarly be condensed with acetophenone and with cyclohexanone to form β-hydroxy esters IB and IIB in yields of 66 and 69%, respectively. Whereas one molecular equivalent of lithium amide was employed with the *t*-butyl ester, two equivalents of this reagent were used with ethyl acetate. The ethyl ester was added to the lithium amide in liquid ammonia, followed after two minutes by the ketone. The condensation was completed in refluxing ether. Under these conditions, no appreciable self-condensation of the ester or acylation of the ketone with the ester occurred. Thus, in a preliminary experiment with ethyl acetate and acetophenone, an alkali extraction of the reaction mixture failed to yield acetoacetic ester or benzoylacetone. Moreover, samples of β-hydroxy esters IV and IIB failed to give the enol test with ferric chloride indicating the absence of the β-keto ester or β-diketone.

We believe that the present method is more convenient to carry out than the Reformatsky reaction which has generally been employed for the synthesis of ethyl β-hydroxy esters such as IB and IIB.

Experimental

Ethyl Acetate with Acetophenone.—To a stirred suspension of 0.42 mole of lithium amide in 500 ml. of anhydrous liquid ammonia[2] was added during one minute, 17.6 g. 0.2 mole) of purified ethyl acetate in 50 ml. of anhydrous ether. After two minutes, 24.0 g. (0.20 mole) of acetophenone in 50 ml. of anhydrous ether was added during one minute. The liquid ammonia was evaporated during 15–20 minutes as 300 ml. of anhydrous ether was being added. After stirring and refluxing for two hours, the reaction mixture was cooled in an ice-bath and decomposed with a mixture of 160 ml. of 3 *N* hydrochloric acid and 80 ml. of ice-water. The ether layer was separated and washed with 1 *N* sulfuric acid, saturated sodium bicarbonate solution, and water, and combined with ether extracts of the aqueous layers. The solution was dried over Drierite and the solvent removed. The residue was distilled *in vacuo* to give 4.65 g. (20%) of recovered acetophenone, b.p. 82–93° at 15 mm., and 27.3 g. (66%) of ethyl β-hydroxy-β-phenylbutyrate (IB), b.p. 146–148° at 15 mm. Only a trace of residue remained.

(1) Supported by the Duke University Research Council.

(2) C. R. Hauser and W. H. Puterbaugh, THIS JOURNAL, **75**, 2972 (1951); *ibid.*, **75**, 1068 (1953).

(3) Analyses by Galbraith Laboratories, Knoxville, Tenn.