

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

#### Experimental<sup>4</sup>

**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  $-30^\circ$  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  $5^\circ$ , 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  $\beta$ -*t*-butylhydrocinnamaldehyde.<sup>5</sup> Attempts to distill 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  $\beta$ -*t*-butylhydrocinnamic acid, a colorless micro-crystalline solid, which was sublimed at  $100$ – $106^\circ$  under a pressure of 0.05–0.01 mm., m.p.  $113.5^\circ$  (cor.). The yield was very low.

*Anal.*<sup>6</sup> Calcd. for  $\text{C}_{13}\text{H}_{18}\text{O}_2$ : 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  $-40^\circ$ . 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  $\beta$ -*t*-butylhydrocinnamic acid in very low yield. It sublimed at  $85$ – $106^\circ$  under a pressure of 0.05–0.01 mm. to give colorless crystals melting at  $90$ – $110^\circ$ . A second sublimation gave the pure acid, m.p.  $113^\circ$ .

*Anal.* Calcd. for  $\text{C}_{13}\text{H}_{18}\text{O}_2$ : 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  $113.5$ – $114^\circ$ . Since this work was completed this acid has been made by the addition of *t*-butylmagnesium chloride to cinnamic acid.<sup>7</sup>

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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.

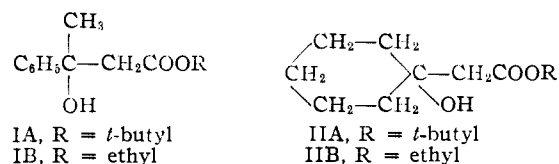
(7) J. H. Wotiz, J. S. Matthews and H. Greenfield, *THIS JOURNAL*, **75**, 6343 (1953).

## Aldol Condensation of Ethyl Acetate with Ketones to Form $\beta$ -Hydroxy Esters by Lithium Amide<sup>1</sup>

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



It has now been found that ethyl acetate may similarly be condensed with acetophenone and with cyclohexanone to form  $\beta$ -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  $\beta$ -hydroxy esters IV and IIB failed to give the enol test with ferric chloride indicating the absence of the  $\beta$ -keto ester or  $\beta$ -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  $\beta$ -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<sup>3</sup> 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.  $82$ – $93^\circ$  at 15 mm., and 27.3 g. (66%) of ethyl  $\beta$ -hydroxy- $\beta$ -phenylbutyrate (IB), b.p.  $146$ – $148^\circ$  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*, **73**, 2972 (1951); *ibid.*, **75**, 1068 (1953).

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

*Anal.*<sup>3</sup> Calcd. for C<sub>12</sub>H<sub>16</sub>O<sub>5</sub>: C, 69.21; H, 7.74. Found: C, 69.12; H, 7.74.

When a mixture of 0.2 mole each of ethyl acetate and acetophenone was added to 0.4 mole of lithium amide in liquid ammonia and the reaction completed in refluxing ether as described above, there was obtained a 47% yield of the  $\beta$ -hydroxy ester.

The  $\beta$ -hydroxy ester was identified by dehydration with phosphorus oxychloride in benzene solution to form ethyl  $\beta$ -methylcinnamate, b.p. 146–149° at 17 mm. (reported 146–148° at 16.5 mm.),<sup>4</sup> and by saponification of the latter ester to give  $\beta$ -methylcinnamic acid, m.p. 97–98° (reported 97–98°).<sup>4</sup>

**Ethyl Acetate with Cyclohexanone.**—This condensation was carried out essentially as described above with acetophenone employing 0.2 mole each of ethyl acetate and cyclohexanone, and 0.42 mole of lithium amide. There was obtained, after a small forerun of cyclohexanone, 25.4 g. (69%) of ethyl 1-hydroxycyclohexyl acetate (IIB), b.p. 124–126° at 18 mm.

*Anal.*<sup>3</sup> Calcd. for C<sub>10</sub>H<sub>18</sub>O<sub>3</sub>: C, 64.49; H, 9.74. Found: C, 64.54; H, 9.80.

The  $\beta$ -hydroxy ester was identified by saponification to form cyclohexanolacetic acid, m.p. 63–64° (reported 62–64°).<sup>5</sup>

(4) S. Lindenbaum, *Ber.*, **50**, 1270 (1917).

(5) O. Wallach, *Ann.*, **347**, 328 (1906).

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### On the Mechanism of the Oxidation of Uric Acid by Alkaline Peroxide<sup>1a</sup>

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The action of alkaline peroxide on uric acid (I) has been studied by several authors,<sup>2a,b</sup> who assigned the following structures to the degradation products, oxonic acid (II) and allantoxaidin (III).

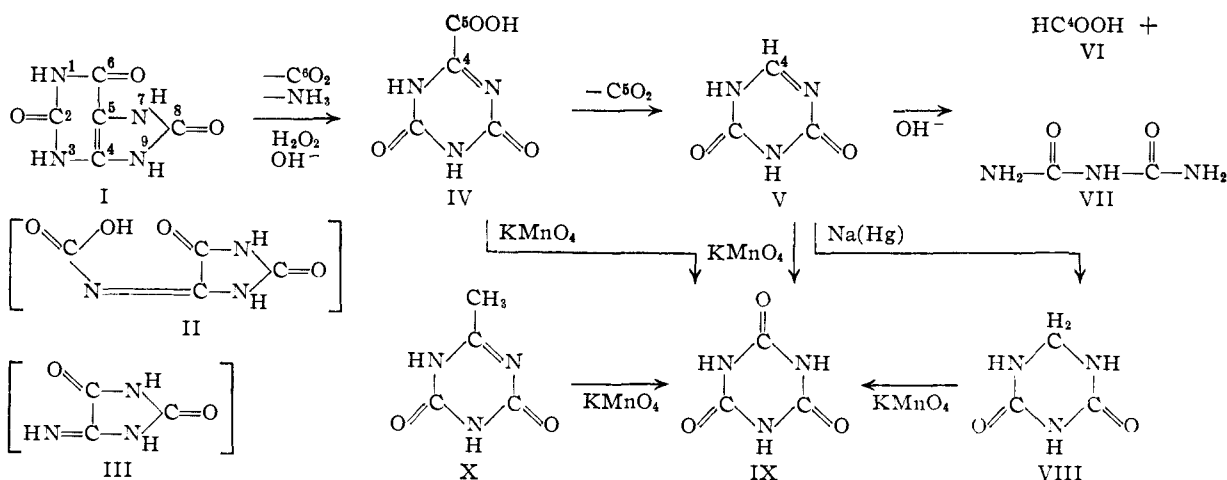


Fig. 1.—Proposed products of the oxidation of uric acid by alkaline peroxide. The numbering of the atoms of the degradation products refers to the numbering of the corresponding atoms in the uric acid molecule.

However, when the reaction was followed with uric acid labeled in positions 2, 4, 6 and 8 with C<sup>14</sup>,

(1) (a) Supported by grants from the Damon Runyon Memorial Fund for Cancer Research, Inc., and the National Cancer Institute, National Institutes of Health, United States Public Health Service. (b) Predoctoral Fellow of the National Science Foundation (1953–1954). The material of this report was submitted in partial fulfillment of the requirements for the degree of Master of Science, Massachusetts Institute of Technology.

(2) (a) C. S. Venable, *THIS JOURNAL*, **40**, 1099 (1918); (b) F. J. Moore and R. M. Thomas, *ibid.*, **40**, 1120 (1918).

it became clear that this scheme could not account for the results.<sup>3</sup> While carbon number 6 appeared in the first molecule of carbon dioxide liberated, carbons 2, 4 and 8 did not act as precursors for the second molecule of carbon dioxide, which therefore must originate from carbon number 5. Because of this and in view of the ease with which oxonic acid can be oxidized to cyanuric acid (IX)<sup>4</sup> and allantoxaidin split to formic acid (VI) and biuret (VII),<sup>2b</sup> Brandenberger<sup>3</sup> proposed structure IV and V for oxonic acid and allantoxaidin, respectively. The present paper reports experiments confirming this hypothesis by a stepwise degradation of uric acid labeled in position 4 with C<sup>14</sup> to biuret and formic acid and by chemical and spectroscopic studies of allantoxaidin and analogs.

The oxonic acid was prepared by a modification of the method of Moore and Thomas<sup>2b</sup> as the potassium salt. This was then transformed into the silver salt which is decarboxylated readily to allantoxaidin in dilute hydrochloric acid. This method permitted an easy separation of the inorganic acid and salt from the reaction products, which would be difficult otherwise. The CO<sub>2</sub> evolved in the preceding steps was collected separately as barium carbonate. The allantoxaidin was hydrolyzed to biuret and formic acid with concentrated ammonia. The results of the degradation experiments on uric acids labeled in positions 4 and 5, respectively, are given in Table I. It is seen that the carboxyl group of oxonic acid is derived from carbon 5 of the uric acid, and that carbon 4 of the uric acid is found *entirely* in the formic acid obtained from the allantoxaidin. The latter observation cannot be explained on the basis of the old reaction mechanism. The results of the above experiments can be ex-

plained readily, however, if oxonic acid and allantoxaidin are assigned the triazine structures IV and V.

Sodium amalgam reduces allantoxaidin to a dihydro derivative of the empirical formula C<sub>3</sub>H<sub>5</sub>O<sub>2</sub>N<sub>3</sub> (VIII). Acid permanganate easily oxidizes this compound to cyanuric acid, a fact which strongly indicates a *s*-triazine structure.

(3) H. Brandenberger, *Helv. Chim. Acta*, **37**, 641 (1954).

(4) H. Biltz and R. Robl, *Ber.*, **54B**, 2441 (1921).