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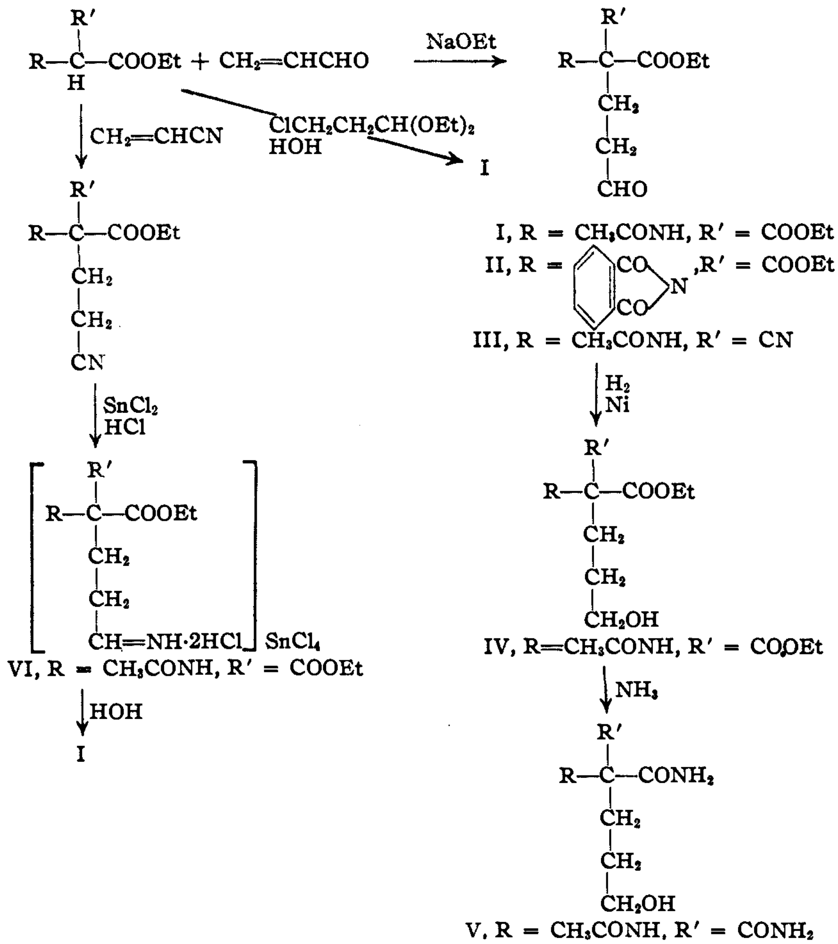
1,4-Addition Reactions. I. The Addition of Acylamidomalonates to Acrolein[1a]

BY OWEN A. MOE AND DONALD T. WARNER

The 1,4-addition reactions between malonate systems and α,β-unsaturated aldehydes have not been reported. Instead, under the conditions employed, a Knoevenagel condensation occurs and the reaction involves a 1,2-addition. However, the latter reaction requires two α-hydrogen atoms for completion (addition followed by loss of water) whereas the former reaction requires only one α-hydrogen atom. Since both reactions, 1,2-addition and 1,4-addition, are reversible, it appeared that a 1,4-addition reaction of acrolein might be realized provided the addend possessed only one, but sufficiently reactive, α-hydrogen atom.



This paper describes the successful 1,4-addition of three such compounds (ethyl acetamidomalonate, ethyl phthalimidomalonate and ethyl acetamidocyanoacetate) to acrolein. The products, obtained in excellent yields, have structures I, II and III, respectively.

The 1,4-addition of ethyl acetamidomalonate to acrolein proceeded smoothly in an alcoholic solution in the presence of catalytic quantities of sodium ethoxide. Because of the exothermic character of the reaction, the acrolein was added at a slow rate to a stirred suspension of ethyl acetamidomalonate. Concentration of the neutralized solution yielded γ-acetamido-γ,γ-dicarbethoxybutyraldehyde I as a straw-colored, viscous oil. The action of phenylhydrazine on either the original reaction mixture or the viscous oil yielded the crystalline phenylhydrazone of compound I in 65–85% yield. The 1,4-addition of ethyl acetamidomalonate to acrolein also proceeded smoothly in the absence of alcohol when benzene was used as the solvent and the phenylhydrazone was obtained in 87% yield directly from the reaction mixture.

The reaction between ethyl phthalimidomalonate and acrolein yielded γ,γ-dicarbethoxy-γ-phthalimidobutyraldehyde II which was characterized as the phenylhydrazone and the 2,4-dinitrophenylhydrazone. Ethyl acetamidocyanoacetate yielded a crystalline adduct (γ-acetamido-γ-carbethoxy-γ-cyanobutyraldehyde) which was characterized as the crystalline 2,4-dinitrophenylhydrazone.

The structure of the aldehydo compound I was proved by two different syntheses. The first method involved the alkylation of ethyl acetamidomalonate with β-chloropropionaldehyde diethylacetal. Hydrolysis of the product with dilute acid gave compound I. In the second synthesis, ethyl α-acetamido-α-carbethoxy-γ-cyanobutyrate[1] was reduced by the action of stannous chloride and hydrogen chloride.[2] The resulting crystalline complex was readily hydrolyzed with warm water to I. As a by-product there resulted a crystalline compound melting at 181–182°. The an-

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(1) Albertson and Archer, THIS JOURNAL, 67, 2043 (1945).

(2) (a) Stephen, *J. Chem. Soc.*, 127, 1874 (1925); (b) Williams, THIS JOURNAL, 61, 2248 (1939).

alysis indicated that this compound was ethyl α-acetamido-α-carbethoxy-γ-carbamylbutyrate.

The aldehydo compound I, subjected to hydrogenation in the presence of Raney nickel, gave the crystalline carbinol IV which was characterized as the 3,5-dinitrobenzoate and the *p*-nitrobenzoate. Action of concentrated ammonia upon IV yielded the diamido compound V which in turn yielded a *p*-nitrobenzoate.

Experimental[3]

The 1,4-Addition of Ethyl Acetamidomalonate to Acrolein. A. In Alcohol.—A mixture containing ethyl acetamidomalonate[4] (87.4 g.), sodium (0.1 g.) and absolute ethanol (200 cc.) was chilled in an ice-bath to 3° to produce a thin slurry. Acrolein (25.9 g.) was added dropwise with stirring over a period of seventy-five minutes while the reaction temperature was maintained at 3–7°. A clear, light yellow solution resulted after an additional hour of stirring. The reaction mixture was allowed to stand for an additional ninety minutes at 3° and then the catalyst was neutralized with glacial acetic acid (0.35 g.). The total volume of the reaction mixture was 290 cc. A portion (135 cc.) of the reaction mixture was treated with 4 g. of acetic acid and 22 g. of phenylhydrazine. After warming to 50° the solution was diluted with 7 cc. of water and cooled overnight. The crystalline product was collected by filtration and dried. The phenylhydrazone (44 g.) thus obtained melted at 135–137°. The filtrate was diluted with water and an additional quantity (6.4 g.) of the phenylhydrazone was obtained. After crystallization from aqueous ethanol the phenylhydrazone melted at 140–141°.

Anal. Calcd. for $C_{18}H_{25}O_5N_2$: C, 59.5; H, 6.94; N, 11.58. Found: C, 59.8; H, 7.17; N, 11.41.

B. In Benzene.—Ethyl acetamidomalonate (217 g.) was suspended in benzene (330 cc.) containing a catalytic amount of sodium methoxide (0.5 g.). The resulting reaction mixture was cooled in a water-bath at 19°. Acrolein (68.5 cc.) dissolved in benzene (70 cc.) was added dropwise at a moderate rate. The temperature increased rapidly to 35°. Following the addition of the acrolein the reaction mixture was stirred for an additional two hours and filtered. The clear, yellow filtrate was treated with 24 cc. of glacial acetic acid and 120 g. of phenylhydrazine. After warming to 50° the resulting orange-colored solution was set aside for a period of two days. The crystalline derivative was collected by filtration and washed with 150 cc. of benzene. It was further decolorized by suspension in 250 cc. of benzene, filtered and dried *in vacuo*. The yield of the phenylhydrazone of the aldehydo compound I was 315.1 g. (87%) melting at 140–141°. The crystals were nearly white in color.

Reduction of γ-Acetamido-γ,γ-dicarbethoxybutyraldehyde.—The crude aldehydo compound (46.9 g.) was dissolved in ethanol and Raney nickel catalyst (4.8 g.) was added. The resulting mixture (290 cc.) was hydrogenated for two and one-half hours at a temperature of 85–95° and an initial pressure of 1700 pounds. After cooling, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. Benzene was added to the residual oil and the solution was again concentrated. This procedure was repeated three times in order to complete removal of the alcohol. Then ether was added and the carbinol IV crystallized from the ether solution. After drying the crystalline product weighed 14.2 g. and melted at 75–77°. Evaporation of the ethereal filtrate yielded additional quantities of the carbinol IV. Purification by recrystallization from ether increased the melting point to 80–81°.

Anal. Calcd. for $C_{12}H_{21}O_6N$: C, 52.36; H, 7.74; N, 5.09. Found: C, 52.62; H, 8.15; N, 5.30.

The 3,5-dinitrobenzoate and the *p*-nitrobenzoate were prepared in the usual manner and after purification melted at 151–152° and 79–80°, respectively.

Anal. Calcd. for $C_{19}H_{22}O_{11}N_2$: C, 48.6; H, 4.95; N, 8.96. Found: C, 48.86; H, 5.40; N, 9.06. Calcd. for $C_{19}H_{24}O_9N_2$: N, 6.61. Found: N, 6.78.

The carbinol IV, ethyl α-acetamido-α-carbethoxy-δ-hydroxyvalerate, was converted to α-acetamido-α-carbamyl-δ-hydroxyvaleramide by treatment with a concentrated ammonia solution (saturated at 0°). The diamido compound V thus obtained melted at 170–171° after recrystallization from ethanol.

Anal. Calcd. for $C_8H_{15}O_4N_3$: C, 44.22; H, 6.96; N, 19.34. Found: C, 44.15; H, 6.91; N, 19.33.

The *p*-nitrobenzoate of the diamido compound V was prepared in the usual manner and it melted at 242–243° with decomposition.

Anal. Calcd. for $C_{15}H_{18}O_7N_4$: N, 15.30. Found: N, 15.25.

Preparation of γ,γ-Dicarbethoxy-γ-Phthalimidobutyraldehyde.—An alcoholic solution containing 90 cc. of absolute ethanol and 60 mg. of sodium was mixed with 20.4 g. of ethyl phthalimidomalonate, and the resulting reaction mixture was cooled to 5°. Acrolein (4.7 cc.) was added dropwise and the temperature of the reaction mixture increased to 20°. After the addition of the acrolein was complete, the reaction mixture was neutralized by the addition of 0.5 cc. of glacial acetic acid, and a nearly colorless solution resulted. The alcoholic solution of the aldehydo compound II was used directly for the preparation of the phenylhydrazone and the 2,4-dinitrophenylhydrazone which melted at 150–151° and 167–168°, respectively.

Anal. Calcd. for $C_{24}H_{25}O_6N_3$: C, 63.84; H, 5.58. Found: C, 64.08; H, 5.89. Calcd. for $C_{24}H_{23}O_{10}N_5$: C, 53.24; H, 4.29; N, 12.94. Found: C, 53.13; H, 4.12; N, 13.15.

Preparation of γ-Acetamido-γ-carbethoxy-γ-cyanobutyraldehyde.—An alcoholic solution containing 60 cc. of absolute ethanol and 50 mg. of sodium was mixed with 17 g. of ethyl acetamidocyanoacetate and the resulting suspension was cooled in a water-bath. Acrolein (7.5 cc.) was added dropwise, and after the addition was complete the reaction was stirred for two hours and finally neutralized with the requisite quantity of glacial acetic acid. The reaction mixture was filtered, and the filtrate was placed in the refrigerator for a period of twenty-four hours when a copious quantity of needle-like crystals was noted. The crystalline product was collected by filtration and dried. The yield of the crude aldehydo compound III was 15 g. melting at 106–109°. Purification by crystallization from 95% ethanol increased the melting point to 113.5–114.5°.

Anal. Calcd. for $C_{10}H_{14}O_4N_2$: C, 53.56; H, 6.29; N, 12.50. Found: C, 53.10; H, 5.93; N, 12.20.

The 2,4-dinitrophenylhydrazone prepared in the conventional manner melted at 196–197° after purification.

Anal. Calcd. for $C_{16}H_{18}O_7N_6$: C, 47.29; H, 4.46; N, 20.69. Found: C, 47.52; H, 4.44; N, 20.86.

When the above addition reaction was carried out using benzene as the reaction diluent, the aldehydo compound III was obtained in 82% yield and melted at 111–112.5°.

Alkylation of Ethyl Acetamidomalonate with β-Chloropropionaldehyde Diethylacetal.—Ethyl acetamidomalonate (10.9 g.) was added to an alcoholic sodium ethoxide solution containing 1.15 g. of sodium and 100 cc. of absolute ethanol. The above reaction mixture was heated to the reflux temperature and β-chloropropionaldehyde diethylacetal[5] (8.3 g.) was added over a ten-minute period. The reflux temperature was maintained for a period of twenty-four hours. The reaction mixture had developed a light orange color. The precipitated sodium chloride was removed after cooling, and the filtrate was concentrated under reduced pressure. The residual oil was clari-

(3) Micro analyses by Mr. Harold Boyd and Miss Katherine Tellor.

(4) Snyder and Smith, THIS JOURNAL, 66, 350 (1944).

(5) Witzemann, Evans, Hass and Schroeder, "Organic Syntheses," 11, 26 (1931).

fied by filtration, and the product thus obtained weighed 11.35 g. and was insoluble in water. A portion (5.2 g.) of the above crude diethylacetal of γ-acetamido-γ,γ-dicarbethoxybutyraldehyde was suspended in 15 cc. of water and 3.5 cc. of 1 *N* sulfuric acid was added. The resulting reaction mixture was warmed over a steam-bath for five to six minutes with vigorous swirling. The insoluble acetal hydrolyzed rapidly to yield a clear, light yellow solution. This solution was treated with 0.5 g. of sodium acetate and concentrated *in vacuo* to a volume of 11 cc. The addition of 33 cc. of ethanol caused an immediate precipitate which was removed by filtration and proved to be inorganic. The clear filtrate was mixed with one cc. of acetic acid and 4.8 cc. of phenylhydrazine. The resulting reaction mixture was heated to 55° and after cooling and diluting with water a crystalline product (0.4 g.) was collected by filtration. The filtrate was further diluted with water and yielded an additional crop of crystals (0.53 g.). The crude phenylhydrazone of the aldehydo compound I thus obtained melted at 128–132° and after crystallization from dilute ethanol it melted at 138–140°. The melting point was not depressed when mixed with the phenylhydrazone prepared by the first method.

Reduction of Ethyl α-Acetamido-α-carbethoxy-γ-cyanobutyrate.—The ethyl α-acetamido-α-carbethoxy-γ-cyanobutyrate was prepared in accordance with the directions given by Albertson and Archer.[1]

Anhydrous stannous chloride (41.6 g.) was suspended in anhydrous ether (320 cc.) and anhydrous hydrogen chloride was passed into the reaction mixture until the formation of two layers was noted. The substituted cyanobutyrate (26.8 g.) was dissolved in 125 cc. of chloroform and the resulting solution was added slowly over a ninety-minute period as the reaction mixture was stirred, and dry hydrogen chloride was passed in for four hours with vigorous stirring. The introduction of the hydrogen chloride was then interrupted; however, the stirring was continued overnight. The following day the introduction of hydrogen chloride was continued for an additional period of eighteen hours at which time a few crystals had appeared. The reaction mixture was then permitted to stand at room temperature for a period of five days. After this total reaction time of one week the aldimine complex had precipitated as a white crystalline product. The complex was collected by filtration, washed with ether and dried *in vacuo* (weight, 65 g.). The odor of hydrogen chloride was noted. A portion of the above complex VI (15 g.) was mixed with 100 cc. of water and warmed to 50°. The clear, aqueous solution which resulted was extracted twice with 100 cc. portions of chloroform. The chloroform extracts were combined and dried over anhydrous sodium sulfate. After filtration the chloroform was removed by distillation *in vacuo* and a viscous oil remained which partially crystallized on standing. This residue was dissolved in a small quantity of ethanol, and a few drops of acetic acid were added together with a slight excess of phenylhydrazine. The resulting reaction mixture was warmed on a steam-bath and after cooling and diluting with water a crystalline product was obtained. The crude phenylhydrazone of the aldehydo compound I melted at 133–137°. After crystallization from dilute ethanol it melted at 138–140°.

The above aqueous solution was again extracted with chloroform. After drying, the chloroform was removed under reduced pressure and a crystalline residue remained. This crude product melted at 135–155° and after crystallization from dilute ethanol it melted at 181–182°. The analysis of this product indicated that it was probably ethyl α-acetamido-α-carbethoxy-γ-carbamylbutyrate.

Anal. Calcd. for $C_{12}H_{20}O_6N_2$: C, 49.97; H, 6.99; N, 9.72. Found: C, 49.84; H, 7.07; N, 9.58.

Summary

1. The 1,4-addition of acylamidomalonates such as ethyl acetamidomalonate, ethyl phthalimidomalonate and ethyl acetamidocyanoacetate to acrolein has been reported.

2. The resulting aldehydo compounds have been characterized as the phenylhydrazones.

3. The structure of γ-acetamido-γ,γ-dicarbethoxybutyraldehyde (resulting from the 1,4-addition of ethyl acetamidomalonate to acrolein) has been proved by two independent synthetic routes.

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Amino Acids. I. New Syntheses of DL-Tryptophan, DL-Ornithine and DL-Glutamic Acid*

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Several syntheses for DL-tryptophan have been reported.[1] Most of these methods employ gramine as the starting material. A different approach was recently disclosed by Hegedus[2] wherein acetoacetic ester was used as the starting material. The present report concerns a new and convenient synthesis of DL-tryptophan employing the phenylhydrazone III of γ-acetamido-γ,γ-dicarbethoxybutyraldehyde I.[3]

The phenylhydrazone III readily underwent cyclization to yield IV, the same product as that obtained by the reaction between gramine and ethyl acetamidomalonate.[1a] The cyclized product IV was converted to DL-tryptophan in the usual way[1a]; the over-all yield based on III was 50%.

Recently, Albertson and Archer[4] published an excellent synthesis of DL-ornithine monohydrochloride in which the cyanoethylation product of ethyl acetamidomalonate was used as an intermediate. The synthesis of DL-ornithine monohydrochloride reported in the present paper involves the phenylhydrazone III as an intermediate. Reduction of III in the presence of Raney nickel gave β-

(*) Paper No. 90, Journal Series, Research Laboratories, General Mills, Inc.

(1) (a) Snyder and Smith, THIS JOURNAL, 66, 350 (1944); (b) Albertson, Archer and Suter, *ibid.*, 66, 500 (1944); 67, 36 (1945); (c) Howe, Zambito, Snyder and Tishler, *ibid.*, 67, 38 (1945); (d) Elks, Elliott and Hems, *J. Chem. Soc.*, 624, 626, 629 (1944).

(2) Hegedus, *Helv. Chim. Acta*, 29, 1499 (1946).

(3) Moe and Warner, THIS JOURNAL, 70, 2763 (1948).

(4) Albertson and Archer, *ibid.*, 67, 2048 (1945).