complex was detected by a considerable increase in ultraviolet absorption at 238 mu. Even if this finding can be extended to the mixed solvents used in this work, we need not necessarily modify the interpretation of the data presented here. For example, the presence of a more effective complexing substance such as EDTA or cysteine would eliminate any competitive effect of tris. The Cu^{II}-tris complex may also show comparable catalytic activity in oxidation reactions. The complex might also rapidly release its Cu^{II} by dissociation as the free Cu^{II} is reduced to Cu^{I}.

TALLAHASSEE, FLORIDA

[CONTRIBUTION FROM THE SCHOOL OF PHARMACY, UNIVERSITY OF NORTH CAROLINA]

Amino Acids. XV. Michael Addition Reactions of Diethyl Acetamidomalonate[1]

BY GEORGE H. COCOLAS[2] AND WALTER H. HARTUNG[3]

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The Michael addition between diethyl acetamidomalonate and ethyl acrylate or ethyl crotonate may give one of two products, depending on the reaction conditions. Mild conditions yield the normal product, whereas reflux temperatures favor the formation of a pyrrolidinone. Pyrrolidinones were also prepared from the normal addition products of diethyl acetamidomalonate or diethyl carbobenzyloxyaminomalonate and the α,β-unsaturated ester. The pyrrolidinones were converted to their corresponding di- and monocarboxylic acids.

The Michael addition of diethyl acetamidomalonate to an appropriate derivative of acrylic acid has become a convenient route to the synthesis of glutamic acid or a suitably substituted glutamic acid.[4-10] However, except for Fillman and Albertson,[6] who noted the loss of a $C_3H_5O_2$ fragment, the intermediates of the reaction or the full path have been ignored. A program calling for the synthesis of analogs and homologs of glutamic acid afforded an opportunity to study both the character of the intermediates and the likely mechanism of the condensation. It soon was apparent that the identity of the adducts depends on the conditions of the reaction. This is true when acrylic and crotonic esters are employed, and it may also apply to esters of other α,β-unsaturated acids.

When the reaction is carried out in the presence of $^1/_{10}$ to $^1/_6$ equivalent of sodium ethoxide under mild conditions, *i.e.*, at either room temperature or in the cold, the normally expected product is formed; but under more strenuous conditions, *i.e.*, at reflux temperatures, a pyrrolidinone derivative forms. These differences may be indicated in Fig. 1.

Support for structure III is afforded by Talbot, Gaudry and Berlinguet,[11] who synthesized IIIa by the reaction between diethyl acetamidomalonate and β-propiolactone and by Kato and his co-workers,[12] who prepared IIIa by the conventional alkylation method from diethyl acetamidomalonate and ethyl β-iodopropionate.

Proof for the pyrrolidinone structures IV was obtained from their preparation by two other methods, namely, (i) formation of IVa and IVb by the

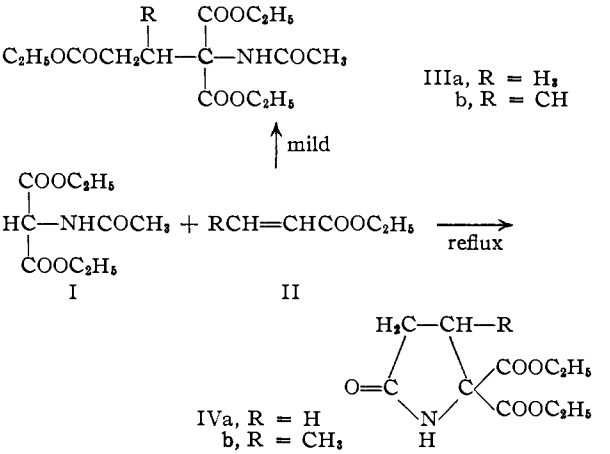

Fig. 1.

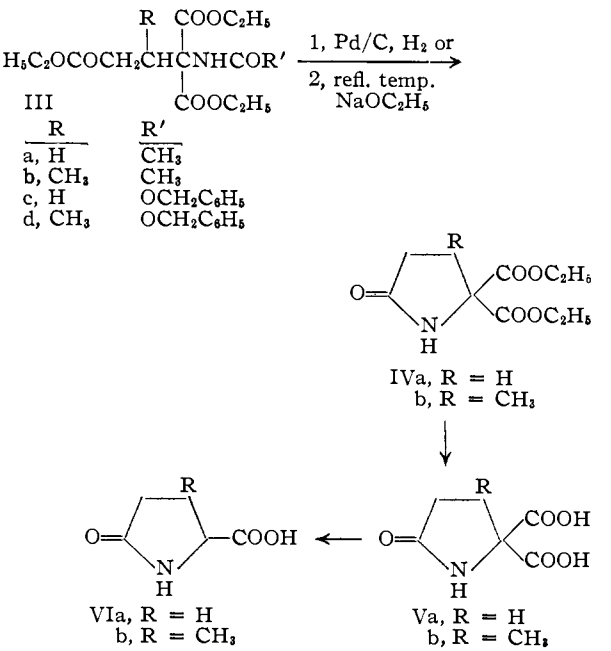

Fig. 2.

(1) For No. XIV see W. H. Hartung, D. N. Kramer and G. Hager, THIS JOURNAL, **76**, 2261 (1954).

(2) Research Laboratories, National Drug Co., Haines and McCallum Streets, Phila. 44, Pa.

(3) School of Pharmacy, Medical College of Virginia, Richmond, Va.

(4) J. Andrako, Ph.D. Thesis, U. of North Carolina, 1953.

(5) N. Albertson and S. Archer, THIS JOURNAL, **67**, 2043 (1945).

(6) J. Fillman and N. Albertson, *ibid.*, **74**, 2969 (1952).

(7) D. Morrison, *ibid.*, **77**, 6072 (1955).

(8) H. Snyder, J. Shekleton and C. Lewis, *ibid.*, **67**, 310 (1945).

(9) A. Meister, L. Levintow, R. E. Greenfield and P. Abendschein, *J. Biol. Chem.*, **215**, 441 (1955).

(10) J. Done and L. Fowden, *Biochem. J.*, **51**, 451 (1952).

(11) G. Talbot, R. Gaudry and L. Berlinguet, *Can. J. Chem.*, **34**, 1440 (1956).

(12) J. Kato, *et al.*, *J. Agr. Chem. Soc. Japan*, **27**, 498 (1953) [*C. A.*, **49**, 3006 (1955)].

synchronous hydrogenolysis and cyclization of IIIc and IIId, respectively, and (ii) by formation of IVa and IVb by refluxing IIIa and IIIb, respectively, in sodium ethoxide.

The pyrrolidinones IV were hydrolyzed to their corresponding dicarboxylic acids V and were subsequently decarboxylated to their monocarboxylic acids VI. IVa and IVb strongly absorb in the infrared near 1692 cm.$^{-1}$, which is characteristic for γ-lactams.

Although it is experimentally possible to transform IIIa and IIIb into IVa and IVb, respectively, as described later, the pyrrolidinone is not a likely intermediate in the mild reaction since alcoholysis of amides is favored at high temperatures. Support for the direct formation of the pyrrolidinones is seen in relative yields from the two procedures; IVa is obtained in yields of 83% when prepared from the reagents at reflux temperatures and in 17% when IIIa is refluxed with sodium ethoxide under similar conditions.

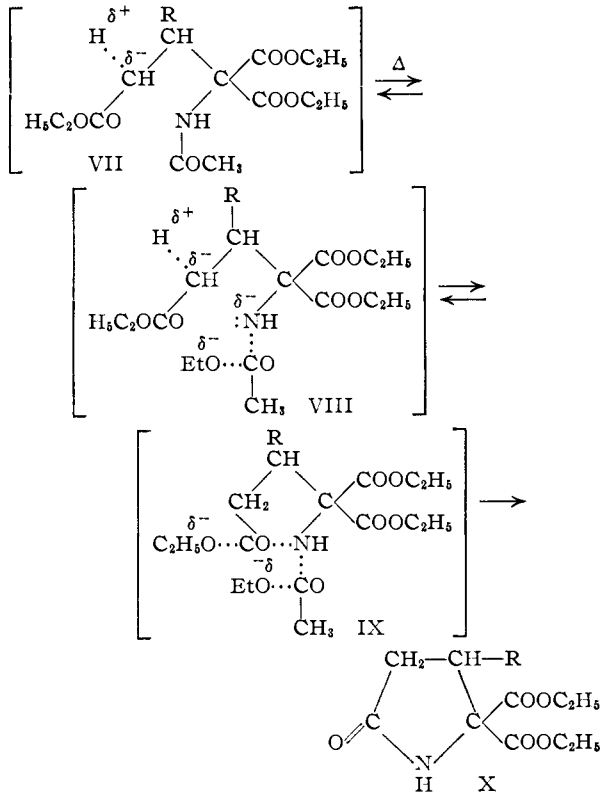

Fig. 3.

Since the formation of a pyrrolidinone from a Michael addition is unexpected, a consideration of a possible manner in which the cyclization occurs may shed light on the feasibility of such a reaction. The occurrence of cyclic products resulting during the course of a Michael addition is not new. Connor and McClellan[13] state that ring closures can occur if the reaction is carried out under reflux conditions. Also, these conditions are favorable for the bimolecular hydrolysis of amides. Therefore it may reasonably be assumed that cleavage of the amide bond can take place under the reflux conditions of the Michael addition. The proposed mechanism is summarized in Fig. 3.

In the presence of ethoxide ions, diethyl acetamidomalonate adds to the α,β-unsaturated ester as in a normal Michael addition to form the intermediate VII.[14] An alcoholysis of the amide occurs under the influence of heat to give VIII. The nitrogen can now attack the γ-carbonyl carbon to give the intermediate IX. This is plausible since the conformation of the molecule places the two groups in question in very close proximity with each other. Furthermore, it has been observed that the cyclization occurs more readily when R is methyl than when it is hydrogen. It is presumed here that the presence of the methyl group in the β-position favors a cyclic conformation, thereby accounting for its greater ease of cyclization compared to the unsubstituted intermediate. The cyclic intermediate IX, being stable, allows the formation of a full bond between nitrogen and the γ-carbonyl carbon with the elimination of ethyl acetate, regeneration of ethoxide ion and formation of the corresponding 5,5-dicarbethoxy-2-pyrrolidinone (X).

Experimental[15]

Diethyl acetamidomalonate was prepared according to the method described by Snyder and Smith.[16]

Diethyl N-Acetyl-α-carbethoxyglutamate (IIIa).—Diethyl acetamidomalonate (10.85 g.) was dissolved in 250 ml. of absolute ethanol containing 115 mg. (0.005 g. atom) of sodium and the solution cooled in an ice-bath. Ethyl acrylate (7.5 g.) was added slowly to prevent an excessive rise in temperature. The mixture was then stirred for 90 minutes and neutralized with glacial acetic acid. After gently removing the ethanol under reduced pressure, the residue crystallized on standing and was recrystallized from acetone–water to give 12.1 g. (76%) of IIIa, m.p. 65–66°. A portion twice recrystallized from acetone–water for analysis gave needles of IIIa, m.p. 66.5–67°, reported[11] 66–67°.

Anal. Calcd. for $C_{14}H_{23}NO_7$: C, 52.99; H, 7.31; N, 4.41. Found: C, 53.28; H, 7.26; N, 4.34.

Diethyl N-Acetyl-α-carbethoxy-β-methylglutamate (IIIb).—Ethyl crotonate (8.4 g.) was added to a solution of diethyl acetamidomalonate (10.85 g.) in absolute ethanol containing 0.115 g. of sodium. The mixture was stoppered and allowed to sit for 7 days before neutralizing with glacial acetic acid. The solvent was removed gently under reduced pressure and the oily residue solidified on standing. This was recrystallized from ethanol–water to give 12.5 g. of IIIb (75.5%). A sample for analysis twice recrystallized from ethanol–water melted at 58°.

Anal. Calcd. for $C_{15}H_{25}NO_7$: C, 54.37; H, 7.61; N, 4.23. Found: C, 54.42; H, 7.63; N, 4.33.

Diethyl N-Carbobenzyloxy-α-carbethoxyglutamate (IIIc) was prepared in the same manner as IIIa. Ethyl acrylate (21.0 g.), diethyl carbobenzyloxyaminomalonate[17] (61.0 g.) and sodium (0.765 g.) in 100 ml. of absolute ethanol gave 77.8 g. of crude IIIc, a red-orange oil; 50 ml. of ether was added to the oil and this washed with two 25-ml. portions of water, dried over anhydrous sodium sulfate and the ether removed by distillation. No attempt was made to distil IIIc as previous experience resulted in decomposition of the product.

Anal. Calcd. for $C_{20}H_{27}NO_8$: N, 3.42. Found: N, 3.26, 3.23.

Further proof of IIIc was obtained by its hydrogenolysis–acetylation to IIIa. Ten grams of IIIc dissolved in 50 ml. of acetic anhydride was shaken for 3 hr. in a Parr apparatus

(13) R. Connor and W. R. McClellan, *J. Org. Chem.*, **3**, 570 (1939).

(14) E. T. Alexander, "Principles of Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1953, p. 149.

(15) Melting points were taken with Anschütz stem immersion thermometers.

(16) H. R. Snyder and C. W. Smith, THIS JOURNAL, **66**, 350 (1944).

(17) J. H. Beaujon and W. H. Hartung, *J. Am. Pharm. Assoc., Sci. Ed.*, **41**, 578 (1952).

with 2.0 g. of an A-150 palladium–charcoal catalyst.[18] Product weighing 5.5 g. was isolated and when recrystallized from acetone–water gave needles, m.p. 64–66°; when mixed with authentic IIIa there was no depression.

Diethyl N-Carbobenzyloxy-α-carbethoxy-β-methylglutamate (IIId).—The method was the same as that employed for IIIb. Isolation was similar to that for IIIc. Ethyl crotonate (17.1 g.) and diethyl carbobenzyloxyaminomalonate (31.0 g.) with sodium (0.360 g.) in 100 ml. of absolute ethanol gave 29.5 g. (68%) of IIId, a non-distillable oil.

Anal. Calcd. for $C_{21}H_{29}NO_8$: N, 3.31. Found: N, 3.97, 4.10.

The identity of IIId, in the absence of satisfactory N-analysis, was confirmed in the manner similar to that employed for IIIc. Crude IIId (17.0 g.) was mixed with 50 ml. of acetic anhydride and 2.0 g. of an A-150 palladium–charcoal catalyst to give 6.4 g. of the corresponding N-acetyl derivative. The product was recrystallized from ethanol–water mixture, m.p. 56–58°. A mixed melting point with IIIc was not depressed.

5,5-Dicarbethoxy-2-pyrrolidinone (IVa). Method 1.—To 200 mg. of sodium in 10 ml. of absolute ethanol was added a solution of 10.85 g. of diethyl acetamidomalonate in 200 ml. of absolute ethanol. The mixture was stirred as 7.5 g. of ethyl acrylate was added slowly and then refluxed over a water-bath for 9 hr.[19] After neutralizing with glacial acetic acid, the ethanol was removed by distillation. Colorless crystals separated from the dark oily residue on standing for 24–48 hr. These were collected and recrystallized from anhydrous ether to give white crystals of IVa contaminated with normal Michael addition product IIIa, 9.5 g., m.p. 79–83°. A sample for analysis was recrystallized twice from benzene–petroleum ether, m.p. 82–83°.

Anal. Calcd. for $C_{10}H_{15}NO_5$: C, 52.39; H, 6.60; N, 6.11. Found: C, 52.73, 52.69; H, 6.38, 6.42; N, 6.10, 6.06.

This product corresponds to the compound reported by Morrison[7] as diethyl N-acetyl-α-carbethoxyglutamate with respect to melting point and elemental analysis.

Method 2.—IIIc (12.2 g.), in 50 ml. of absolute ethanol mixed with 2.0 g. of an A-100[18] palladium–charcoal catalyst, was shaken for 3 hr. in a low pressure Parr apparatus at an initial pressure of 60 pounds. The catalyst was removed and the solvent evaporated. The yellow oil remaining solidified on standing. The crystals were collected and washed with petroleum ether, 5.1 g. (74.3%), m.p. 78–80°. Recrystallization from benzene–petroleum ether gave a product melting at 82–83°. A mixed melting point with IVa prepared by method 1 was not depressed.

Method 3.—IIIa (12.0 g.) was refluxed 8 hr. in a solution of sodium (100 mg.) in 100 ml. of absolute ethanol and then neutralized with glacial acetic acid. The solvent was distilled and the oily residue allowed to solidify. The crude product was recrystallized twice from anhydrous ether to give 1.5 g. of white crystals of IVa, m.p. 82–83°. A mixed melting point with IVa obtained by method 1 was not depressed.

The 5,5-Dicarbethoxy-4-methyl-2-pyrrolidinone (IVb). Method 1.—The reaction employed was similar to that described in method 1 for the preparation of IVa. The interaction of 21.7 g. of diethyl acetamidomalonate and 17.1 g. of ethyl crotonate was carried out in 100 ml. of absolute ethanol containing 400 mg. of sodium. The oily residue obtained was steam distilled for 1 hr. Cooling of the steam condensate in the reaction flask precipitated needle-like crystals. The filtrate on subsequent concentrations yielded several crops. The fractions were combined, 24.4 g. (88%), m.p. 76–78°. A sample for analysis twice recrystallized from water melted at 77.5–78°.

Anal. Calcd. for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.39, 54.15; H, 6.86, 6.94; N, 5.75, 5.85.

This product corresponds to the product reported by Morrison[7] as diethyl N-acetyl-α-carbethoxy-β-methylglutamate with respect to melting point and elemental analysis.

Method 2.—The procedure was the same as that used in method 2 for the preparation of IVa. IIId (10.0 g.) in 50 ml. of absolute ethanol and 2.0 g. of an A-150 palladium–charcoal catalyst yielded 1.5 g. of IVb which when recrystallized from water melted at 77–78°. A mixed melting point with IVb made by method 1 was not depressed.

Method 3.—The procedure was the same as method 3 for IVa. IIIb (5.0 g.) was refluxed for 9 hr. in a solution of sodium (100 mg.) and absolute ethanol (100 ml.). The oily residue obtained was boiled with 25 ml. of water. Cooling yielded 2.5 g. (63%) of IVb, m.p. 76–78°. A mixed melting point with IVb obtained by method 1 was not depressed.

5,5-Dicarboxy-2-pyrrolidinone (Va).—To a solution of IVa (5.0 g.) in 25 ml. of absolute ethanol was added 30 ml. of 20% alcoholic potassium hydroxide. Although a precipitate formed almost immediately, the reaction was refluxed over a water-bath for 4 hr. and allowed to sit overnight. The mixture was then cooled to 0° and the precipitate collected, dissolved in 20 ml. of water and filtered free of insoluble material. The clear aqueous solution was cooled to 5° and made acid to congo red with cold concentrated hydrochloric acid. On sitting in a refrigerator for 24 hr., 1.05 g. of Va precipitated. To the filtrate was added one-half its volume of 95% ethanol and the potassium chloride filtered off. The filtrate was carefully concentrated to 10 ml. and cooled to 0–5° to precipitate 0.7 g. more of the desired product. Another such concentration yielded 1.1 g. more of Va. The three batches were combined, 2.85 g. (75.7%). The crystals were decolorized by Norite. A sample recrystallized from water for analysis decomposed without charring and melted at 152.5–153°.

Anal. Calcd. for $C_6H_7NO_5$: N, 8.09; neut. equiv., 86.6. Found: N, 7.97, 7.97; neut. equiv., 86.1, 86.8.

5,5-Dicarboxy-4-methyl-2-pyrrolidinone (Vb).—The same procedure as above was used in the preparation of Va. IVb (3.0 g.) dissolved in 10 ml. of absolute ethanol and refluxed with 20 ml. of 20% alcoholic potassium hydroxide gave, on acidification of the aqueous solution of the di-salt with cold concentrated hydrochloric acid, 1.80 g. (77%) of Vb. A sample twice recrystallized from water melted and decomposed without charring at 152.5°.

Anal. Calcd. for $C_7H_9NO_5$: N, 7.48; neut. equiv., 93.6. Found: N, 7.43, 7.45; neut. equiv., 93.6, 93.2.

5-Carboxy-2-pyrrolidinone (VIa).—One gram of Va was heated on an oil-bath at 150–160° for 4 hr. The flask was cooled to add 10 ml. of water and the water then brought to a boil for a few minutes. The solution was filtered while hot and then decolorized with Norite. Cooling of the filtrate precipitated 0.43 g. of VIa. A sample twice recrystallized from water melted at 180–183°.

Anal. Calcd. for $C_5H_7NO_3$: N, 10.85; neut. equiv., 129.1. Found: N, 10.58, 10.42; neut. equiv., 132.6, 132.3.

5-Carboxy-4-methyl-2-pyrrolidinone (VIb).—The procedure for the preparation of VIa was used. Vb (1.8 g.) gave 0.85 g. of VIb. After several recrystallizations from water a sample was obtained for analysis, m.p. 148–152°.

Anal. Calcd. for $C_6H_9NO_3$: N, 9.79; neut. equiv., 143.1. Found: N, 9.73, 9.61; neut. equiv., 143.8, 143.8.

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(18) W. D. Cash, *et al.*, *J. Org. Chem.*, **21**, 999 (1956).

(19) A small amount of an insoluble amorphous substance usually precipitates in the course of these condensations, especially when reflux conditions are used. Its highly insoluble nature is indicative of it being a polymerization product. The substance is easily removed by filtration.