[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, CORNELL MEDICAL COLLEGE AND FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY]

BIOTIN. X. SYNTHESIS OF *dl*-2-KETO-4-METHYL-2,3,4,6-TETRAHYDRO-1-THIENO[3,4]IMIDAZOLE

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The synthesis of *dl*-dehydrobiotin was described in paper IX of this series (1). Before the synthesis was undertaken, however, it was thought advisable to investigate the reactions on a model substance, 2-keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole (V), in order to determine the feasibility for the preparation of dehydrobiotin.

The starting material, the azlactone of α-benzamidocrotonic acid (I) has been prepared by Carter and others (2) from the reaction between N-benzoylthreonine and derivatives and benzoyl chloride, and by the condensation of acetaldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate. Although the first method gives good yields it is rather long. In the second method it has now been found possible by slightly modifying the procedure of Carter and co-workers to increase the yield from 18–21% to 47%.

When the azlactone I was treated with ethyl thioglycolate and absolute ethanol in the presence of piperidine, the mercaptan added to the α,β-double bond, the azlactone ring opened and the carboxyl group was esterified; this gave in one step 76% of ethyl α-benzamido-β-carbethoxymethylthiobutyrate (II) as an oil.[1]

The thioether II was found to undergo the Dieckmann reaction in the presence of sodium ethoxide and ether to give 2-methyl-3-benzamido-4-keto-5-carbethoxythiophane (III) in 31% yield as a gum. The β-keto ester III gave a green color with an alcoholic solution of ferric chloride and was characterized as the 2,4-dinitrophenylhydrazone.

When III was refluxed with a mixture of acetic and hydrochloric acids the carbethoxyl and N-benzoyl groups were eliminated. From the reaction mixture were isolated crystals of 2-methyl-3-amino-4-ketothiophane hydrochloride (IV) which, without further purification, upon treatment with potassium cyanate in water, deposited crystals of 2-keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]-imidazole (V). The yield of V was 16% from III.

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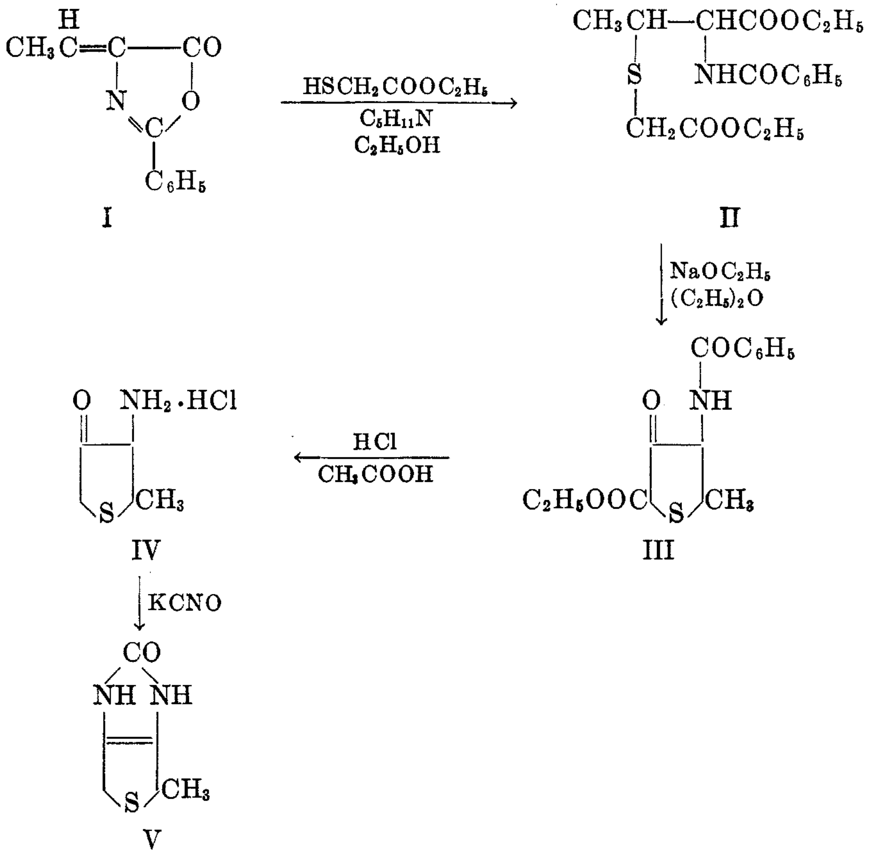
[1] Similar reactions have been reported in the literature. Nicolet (3) treated the azlactone of α-benzamidocinnamic acid with *p*-tolylmercaptan and ethanol in the presence of sodium ethoxide and obtained ethyl α-benzamido-β-(*p*-tolylmercapto)-β-phenylpropionate. More recently, Carter and others (4) added benzylmercaptan and methanol to the azlactone I in the presence of sodium methoxide and obtained methyl α-benzamido-β-benzylmercaptobutyrate.



EXPERIMENTAL

Azlactone of α-benzamidocrotonic acid (I). The following modification of the procedure of Carter and co-workers (2) was found to produce the best results: To a stirred, 25° mixture of 35.8 g. of hippuric acid, 16.4 g. of anhydrous sodium acetate and 100 cc. of acetic anhydride was added, during one-half hour, 100 cc. of freshly distilled acetaldehyde. The mixture was then warmed to 60° and stirred continuously for eleven hours, whereupon it was poured into ice and water. The resulting solid was filtered and washed with water. The crude wet azlactone was dissolved in the minimum amount of warm ether, the water layer was removed, the ether solution was dried with magnesium sulfate, filtered, and the filtrate was cooled in a dry-ice-acetone bath. The azlactone separated as nearly colorless crystals. After one more recrystallization from ether, 17.6 g. (47%) of practically pure I was obtained; m.p. 88–91°.

Ethyl α-benzamido-β-carbethoxymethylthiobutyrate (II). A solution of 12.7 g. of I and 8.2 cc. of ethyl thioglycolate in 100 cc. of ethanol was treated with five drops of piperidine, allowed to stand at 25° for three days, then refluxed seventy-five minutes, and finally evaporated to dryness at 50°/1 mm. The residual light brown oil was dissolved in ether, washed five times with ice-cold 10% sodium bicarbonate solution, three times with saturated salt solution, dried with magnesium sulfate, and evaporated to dryness. The yield of II as a light brown oil was 18.2 g. (76%).

Anal. Calc'd for $C_{17}H_{23}NO_5S$: C, 57.8; H, 6.5; N, 4.0.
Found: C, 58.5; H, 5.6; N, 4.5.

2-Methyl-3-benzamido-4-keto-5-carbethoxythiophane (III). A mixture of sodium ethoxide prepared from 0.59 g. of sodium, 4.5 g. of II, and 150 cc. of dry ether was shaken at 5° for two hours and at room temperature for sixteen hours. The mixture was cooled to 5° and extracted with several portions of iced water. The aqueous extracts were acidified as rapidly as possible with cold, dilute acetic acid. The resulting emulsion was saturated with salt and extracted with ether. The ether solution was washed with cold 10% bicarbonate solution followed by saturated salt solution, dried with magnesium sulfate, treated with Norit, filtered, and the filtrate was evaporated to dryness. The keto ester III was obtained as an amber oil; yield 1.2 g. (31%).

Anal. Calc'd for $C_{15}H_{17}NO_4S$: C, 58.7; H, 5.5; N, 4.6.
Found: C, 58.5; H, 6.6; N, 4.4.

The keto ester gives a green color with alcoholic ferric chloride, is soluble in cold, dilute alkali, and forms a *2,4-dinitrophenylhydrazone* upon treatment in alcohol with a solution of 2,4-dinitrophenylhydrazine in alcohol and hydrochloric acid. The m.p. of the dinitrophenylhydrazone is 210–213°.

Anal. Calc'd for $C_{21}H_{21}N_5O_7S$: C, 51.8; H, 4.3; N, 14.4.
Found: C, 52.0; H, 4.2; N, 14.6.

2-Keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole (V). A mixture of 0.95 g. of III, 6 cc. of acetic acid, and 6 cc. of 6 *N* hydrochloric acid was refluxed five hours, cooled to 25°, diluted with 25 cc. of water, and extracted several times with ether. The aqueous layer was treated with Norit, filtered, and the filtrate was evaporated to dryness *in vacuo* at 50°. The crystalline residue was dissolved in ethanol, treated with Norit, filtered, and the filtrate was evaporated to dryness *in vacuo*. The residue consisted of 0.25 g. of tan crystals of *2-methyl-3-amino-4-ketothiophane hydrochloride (IV)*.

A solution of 200 mg. of IV in 3 cc. of water was treated with Norit and filtered. The resulting water-white solution was treated with 200 mg. of potassium cyanate. The latter dissolved readily and colorless crystals of V separated rapidly. After ten minutes the product was filtered and washed with 1 cc. of water; m.p. 172–175° (dec.); yield 55 mg. (16% from III).

Anal. Calc'd for $C_6H_8N_2OS$: C, 46.2; H, 5.1; N, 17.9; S, 20.5.
Found: C, 46.1; H, 5.7; N, 18.4; S, 20.5.

SUMMARY

A synthesis of *dl*-2-keto-4-methyl-2,3,4,6-tetrahydro-1-thieno[3,4]imidazole is described, which involves Dieckmann cyclization of ethyl α-benzamido-β-carbethoxymethylthiobutyrate, acid hydrolysis of the keto ester so obtained, and treatment of the resultant 2-methyl-3-amino-4-ketothiophane hydrochloride with potassium cyanate.

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