hydrochloric acid solution to give 4-benzamido-3-ketotetrahydrothiophene, IV.

The valeric acid side chain was introduced by means of an aldehyde prepared from glutaric acid.[9] The acid was converted in turn to glutaric anhydride, glutaric acid monomethyl ester, γ-carbomethoxybutyryl chloride,[10] V, and finally to methyl γ-formylbutyrate by a Rosenmund reduction.[11]

The aldehyde ester, VI, condensed with the ketone, IV, when piperidine acetate was used as the catalyst, to yield the methyl ester of 4-benzamido - 3 - keto - $\Delta^{2,5}$ - tetrahydro - 2 - thiophenevaleric acid, VII, m. p. 116° (*Anal.* Calcd. for $C_{17}H_{19}NO_4S$: C, 61.24; H, 5.74; N, 4.20. Found: C, 61.37; H, 6.05; N, 4.17). This unsaturated ketone, VII, reacted with hydroxylamine hydrochloride in pyridine to yield the methyl ester of 4-benzamido-3-oximino-$\Delta^{2,5}$-tetrahydro-2-thiophenevaleric acid, VIII. The unsaturated oxime, VIII, was reduced in an acetic acid-acetic anhydride mixture with zinc dust. Two dehydro compounds were obtained, m. p. 185–186° and m. p. 162–163°. One of these, m. p. 185–186°, is the methyl ester of 3-acetamido-4-benzamido-4,5-dihydro-2-thiophenevaleric acid, IX (*Anal.* Calcd. for $C_{19}H_{24}N_2O_4S$: C, 60.61; H, 6.42; N, 7.43; S, 8.52. Found: C, 60.79; H, 6.33; N, 7.45; S, 8.86). The position of the double bond in this compound will be discussed in a later paper.

This dehydro compound, IX, was hydrogenated over a palladium catalyst. By fractional crystallization of the products, two racemates, m. p. 153–154° (*Anal.* Calcd. for $C_{19}H_{26}N_2O_4S$: C, 60.29; H, 6.92; N, 7.43. Found: C, 60.40; H, 6.92; N, 7.32) and m. p. 172–173°, of the methyl ester of 3-acetamido-4-benzamidotetrahydro-2-thiophenevaleric acid, X, were obtained. After hydrolysis of each of these diamido esters, X, with barium hydroxide, as was done with biotin,[12] and subsequent treatment with sulfuric acid, the corresponding sulfates of the 3,4-diaminotetrahydro-2-thiophenevaleric acids were obtained. Treatment of these diamino acids, XI, with phosgene[13] yielded two racemates of hexahydro - 2 - oxo - 1 - thieno[3, 4]imidazole - 4 - valeric acid, XII, which will be called *dl*-biotin, m. p. 232°, and *dl*-allobiotin, m. p. 194–196°. *dl*-Biotin was derived from the diamido ester, X, melting at 153–154°. *dl*-Biotin was resolved through its esters with *l*-mandelic acid to give biotin.[2]

(9) "Organic Syntheses," Coll. Vol. I, 2nd ed., p. 289 (1941).
(10) Clutterbuck and Raper, *Biochem. J.*, **19**, 385 (1925).
(11) "Organic Syntheses," **21**, 84 (1941).
(12) Hofmann, Melville and du Vigneaud, *J. Biol. Chem.*, **141**, 207 (1941).
(13) Melville, Hofmann and du Vigneaud, *Science*, **94**, 308 (1941).

RAHWAY, NEW JERSEY RECEIVED AUGUST 29, 1944

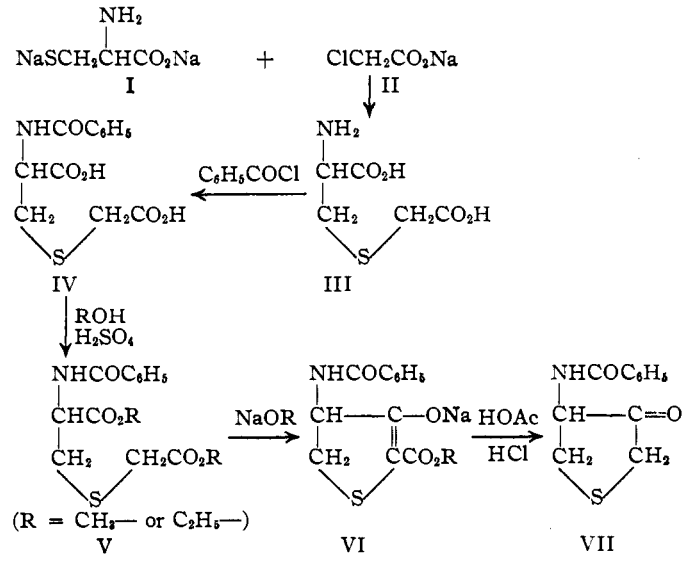
[CONTRIBUTION FROM THE RESEARCH LABORATORY OF MERCK & CO., INC.]

Biotin. IV. Synthesis of 4-Benzamido-3-ketotetrahydrothiophene

BY STANTON A. HARRIS, NELSON R. EASTON, DOROTHEA HEYL, ANDREW N. WILSON AND KARL FOLKERS

A summary of the reactions used in the total synthesis of biotin was given in a previous communication.[1] The synthesis of the 4-benzamido - 3 - ketotetrahydrothiophene, which is a key intermediate in this synthesis, was obtained by the reactions described in this paper.

l-Cystine, or *l*-cysteine, and chloroacetic acid are the primary starting materials for this synthesis. *l*-Cysteine and chloroacetic acid were condensed previously[2] in alkaline solution to give β-(carboxymethylmercapto)-alanine, III. The benzoylation and esterification to compounds IV and V were accomplished without racemization. The ring closure of the ester, V, was a very facile reaction, since it took place in methanol at room temperature by adding sodium methoxide. After a few seconds, the crystallization of the sodium salt, VI, commenced and the reaction was



(1) Harris, Wolf, Mozingo, Anderson, Arth, Easton, Heyl, Wilson and Folkers, THIS JOURNAL, **66**, 1756 (1944).
(2) (a) Michaelis and Shubert, *J. Biol. Chem.*, **106**, 331 (1934); (b) Blood and Lewis, *ibid.*, **139**, 407 (1941).

complete in a few minutes. By careful acidification, the sodium salt was converted to the keto ester, which was hydrolyzed and decarboxylated in an aqueous mixture of acetic acid and hydrochloric acid to give 4-benzamido-3-ketotetrahydrothiophene, VII. The Dieckmann ring closure resulted in racemization of the product, since the keto ester and the ketone were optically inactive.

The synthesis of this ketone, VII, was accomplished also with serine as the starting material. N-Benzoylserine[3] was esterified and treated with thionyl chloride to give the ethyl ester of N-benzoyl-β-chloroalanine, VIII, which was coupled

$$\underset{\text{VIII}}{\text{ClCH}_2\text{CHCO}_2\text{C}_2\text{H}_5}\ (\text{HNCOC}_6\text{H}_5) + \text{NaSCH}_2\text{CO}_2\text{C}_2\text{H}_5 \longrightarrow \text{V (R = C}_2\text{H}_5)$$

with the sodium salt of thioglycolic ester to give the diethyl ester of β-(carboxymethylmercapto)-alanine, V (R = C_2H_5). This ester in ethyl alcohol solution in the presence of sodium ethoxide gave the sodium salt of the keto ester, VI (R = C_2H_5). After hydrolysis and decarboxylation, the product was found to be identical with the ketone, VII, described above.

The condensation of this ketone with aldehydes,[1] and other reactions leading to the synthesis of biotin will be described in the next paper.

Experimental Part

l-β-(Carboxymethylmercapto)-alanine, III.—This compound was prepared by a variation of the method of Blood and Lewis.[2b] *l*-Cystine (265 g.) was added slowly with stirring to a solution of 200 g. of sodium in 3–3.5 liters of liquid ammonia, contained in a Dewar flask, until the blue color had disappeared. The reaction mixture was poured into a large evaporating dish, and the ammonia allowed to evaporate. The residue was dissolved in 1 liter of water and an aqueous solution of 202 g. of chloroacetic acid was added slowly. After one-half hour, the solution was acidified to litmus with glacial acetic acid and cooled. Unchanged cystine was removed by filtration and the liquor was made just acid to congo red with concentrated hydrochloric acid. When the solution was allowed to stand, the product crystallized. Four runs using 265 g., 137 g., 132 g. and 272 g. of *l*-cystine gave a total of 980 g. (82.2%) of product; m. p. 192°.

When *l*-cysteine and chloroacetic acid were used to make the alanine derivative, III, by the method of Michaelis and Shubert,[2a] but with ten-fold their quantities, the yield was increased from 70% to 88%. However, the melting point of 193–194° agreed more closely with that reported by Blood and Lewis.[2b]

Anal. Calcd. for $C_5H_9O_4NS$: C, 33.51; H, 5.06; N, 7.82. Found: C, 33.57; H, 5.13; N, 7.64.

l-N-Benzoyl-β-(carboxymethylmercapto)-alanine, IV.—A solution of 150 g. of β-(carboxymethylmercapto)-alanine and 175 g. of sodium hydroxide in 1500 cc. of water was cooled with an ice-bath and 196 cc. of benzoyl chloride was added with stirring at such a rate that the temperature of the reaction mixture stayed below 20°. After the mixture came to room temperature, it was poured into 365 cc. of concentrated hydrochloric acid and some ice. The solid was extracted with ether. The extract was concentrated and the residue extracted with benzene to remove benzoic acid. The yield of crude *l*-N-benzoyl-β-(carboxymethylmercapto)-alanine from three such batches was 475 g. (67%). A sample was recrystallized from ethyl acetate and petroleum ether (30–60°); m. p. 139–140°; $[\alpha]^{25}D$ −77° in methanol (*c*, 2.52).

Anal. Calcd. for $C_{13}H_{13}O_5NS$: C, 50.87; H, 4.62; N, 4.94. Found: C, 50.82; H, 4.64; N, 4.87.

l-N-Benzoyl-β-(carbomethoxymethylmercapto)-alanine Methyl Ester, V.—A solution of 475 g. of crude N-benzoyl-β-(carboxymethylmercapto)-alanine, 1000 cc. of methanol and 10 cc. of concentrated sulfuric acid was refluxed for five hours. It was then cooled and 3 liters of water was added. The layers were separated and the aqueous layer was extracted with benzene. The extract was washed with water, sodium bicarbonate solution and again with water. After drying with sodium sulfate and distillation of the benzene, the sirupy ester weighed 378 g. (72.5%). A sample of the *l*-N-benzoyl-β-(carbomethoxymethylmercapto)-alanine methyl ester, crystallized from benzene by the gradual addition of petroleum ether (30–60°), melted at 63–64°, $[\alpha]^{25}D$ −76° in methanol (*c*, 1.47).

Anal. Calcd. for $C_{14}H_{17}O_5NS$: C, 54.00; H, 5.51; N, 4.50. Found: C, 54.13; H, 5.32; N, 4.47.

Sodium Salt of *dl*-4-Benzamido-3-ketotetrahydro-2-thiophenecarboxylic Acid Methyl Ester, VI.—To a solution of 770 g. of sirupy ester, V, in 500 cc. of methanol, was added a solution of 57 g. of sodium in 100 cc. of methanol, whereupon the sodium salt of 4-benzamido-3-ketotetrahydro-2-thiophenecarboxylic acid methyl ester crystallized immediately. After one hour, the sodium salt was removed by filtration, washed with methanol and ether, and air-dried; yield 663 g. (89%). Because of its apparent instability, it was used within twenty-four hours.

Anal. Calcd. for $C_{13}H_{12}O_4NSNa$: C, 51.82; H, 4.02; N, 4.65; S, 10.64. Found: C, 51.67; H, 4.03; N, 4.57; S, 10.10, 9.88.

***dl*-4-Benzamido-3-ketotetrahydrothiophene, VII.**—The sodium salt, VI, (332 g.) was dissolved by heating in 1980 cc. of an acid mixture containing 5 volumes of 50% aqueous acetic acid and 1 volume of concentrated hydrochloric acid. The solution was diluted with 275 cc. of water and refluxed in an oil-bath at 135–140° for twenty-five minutes until the decarboxylation was completed. After cooling and seeding, the product was separated by filtration. The mother liquors were extracted with chloroform. The extract was concentrated and the residue was recrystallized twice from alcohol. The total yield of *dl*-4-benzamido-3-ketotetrahydrothiophene was 169.7 g. (76.5%); m. p. 128–129°. It was optically inactive in chloroform and methanol.

Anal. Calcd. for $C_{11}H_{11}O_2NS$: C, 59.70; H, 5.01; N, 6.33. Found: C, 59.85, 59.69; H, 5.07, 5.09; N, 6.40.

***dl*-4-Benzamido-3-ketotetrahydro-2-thiophenecarboxylic Acid Methyl Ester.**—A suspension of 3 g. of the sodium salt, VI, in water was cooled in an ice-bath and acidified with an excess of hydrochloric acid. The semi-solid mass was dissolved in ether, dried with sodium sulfate and concentrated. After standing in ether, a small yield of crystals of *dl*-4-benzamido-3-ketotetrahydro-2-thiophenecarboxylic acid methyl ester appeared and was recrystallized from benzene; m. p. 102–103°.

Anal. Calcd. for $C_{13}H_{13}O_4NS$: C, 55.90; H, 4.69; N, 5.02. Found: C, 56.69, 56.60; H, 4.99, 4.89; N, 4.84.

***dl*-N-Benzoyl-β-(carbomethoxymercapto)-alanine.**—A solution of 1.5 g. of the sodium salt, VI, in warm water was cooled and acidified to congo red with dilute sulfuric acid. An oil separated which was extracted with chloroform and dried. The residue from the chloroform crystallized on trituration with benzene and was recrystallized from benzene; m. p. 108–109°; yield 1.15 g. (82%). From the analysis, it was concluded that the cyclic β-keto ester had been hydrolyzed to give *dl*-N-benzoyl-β-(carbomethoxymercapto)-alanine.

Anal. Calcd. for $C_{13}H_{15}O_5SN$: C, 52.50; H, 5.05; N, 4.71. Found: C, 52.84; H, 5.06; N, 4.58.

Ethyl Ester of *dl*-N-Benzoylserine.—A mixture of 5 g. of N-benzoylserine,[3] 100 cc. of absolute ethyl alcohol, and

(3) Sorenson and Anderson, *Z. physiol. Chem.*, **56**, 297 (1908).

0.75 cc. of concentrated sulfuric acid was refluxed for two hours. After the addition of 1 cc. of water, solid sodium bicarbonate was added until the mixture was neutral to congo red. The filtered solution was concentrated to dryness under reduced pressure, and the residue was taken up in benzene which was distilled to remove water. The dried residue was extracted with absolute alcohol. The solution was filtered, evaporated to dryness, and the ethyl ester of *dl*-N-benzoylserine[4] was crystallized from benzene-petroleum ether; m. p. 79.5–80.5°; yield 3.7 g. (65%).

Ethyl Ester of *dl*-N-Benzoyl-β-chloroalanine, VIII.—A suspension of 1.3 g. of the ethyl ester of *dl*-N-benzoylserine in benzene was treated with 0.4 cc. of dry pyridine and with 0.6 cc. of thionyl chloride and was heated on a steam-bath for twenty minutes. After cooling, the solution was washed with water, dilute hydrochloric acid, saturated sodium bicarbonate solution, and again with water. The benzene was removed under reduced pressure and the ethyl ester of *dl*-N-benzoyl-β-chloroalanine was crystallized from ether–petroleum ether; m. p. 90.5–91.0°; yield, 0.9 g. (67%).

Anal. Calcd. for $C_{12}H_{14}O_3NCl$: C, 56.36; H, 5.52; N, 5.48. Found: C, 56.80; H, 5.15; N, 5.37.

Ethyl Ester of *dl*-N-Benzoyl-β-(carboethoxymethylmercapto)-alanine, V (R = C_2H_5).—A solution of 0.85 g. of ethyl thioglycolate in 4 cc. of 12% sodium ethoxide solution was added to a solution of 1.8 g. of the ethyl ester of *dl*-N-benzoyl-β-chloroalanine in a few cubic centimeters of absolute alcohol. After heating on the steam-bath for thirty minutes, the mixture was neutral to litmus. The precipitated sodium chloride was removed by filtering, and the alcohol was distilled under reduced pressure. The residue was taken up in ether. The solution was filtered to remove sodium chloride, and the ether was evaporated leaving the ester as an oil.

(4) Erlenmeyer, *Ber.*, **35**, 3769 (1902).

***dl*-4-Benzamido-3-ketotetrahydrothiophene.**—Ring closure of the crude ethyl ester from the preceding experiment with sodium ethoxide in ethyl alcohol gave 1.1 g. (50%) of the sodium salt of *dl*-4-benzamido-3-ketotetrahydro-2-thiophenecarboxylic acid ethyl ester. After hydrolysis and decarboxylation, the yield of *dl*-4-benzamido-3-ketotetrahydrothiophene was 0.5 g. (70%). This compound showed no depression of the melting point when mixed with ketone prepared from cysteine.

Acknowledgments.—The authors wish to thank Messrs. D. F. Hayman, R. N. Boos, W. R. Reiss and H. S. Clark for the microanalyses reported in this paper.

Summary

dl-4-Benzamido-3-ketotetrahydrothiophene, which is a key intermediate in the synthesis of biotin, has been synthesized from *l*-cysteine and chloroacetic acid, and from *dl*-serine and thioglycolic acid.

RAHWAY, NEW JERSEY RECEIVED SEPTEMBER 2, 1944

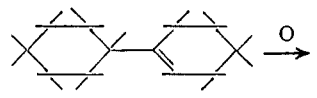
[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

The Polymerization of Cyclohexene with Hydrogen Fluoride

BY S. M. MCELVAIN AND JAMES W. LANGSTON[1]

In connection with a study of the action of hydrogen fluoride on various classes of organic compounds,[2] an investigation of the products formed from the polymerization of cyclohexene was undertaken. Of all of the olefins that can be polymerized by hydrogen fluoride, cyclohexene seemed especially suited to such an investigation because the characterization of its polymers might be facilitated by dehydrogenation to aromatic structures.

There are numerous reports of the polymerization of cyclohexane in the literature. Truffault[3] obtained the dimer (I) in high yields (80–90%) by the action of phosphorus pentoxide on the olefin. The dimer was characterized by oxidation to δ-hexahydrobenzoylvaleric acid (II). Hofmann[4] reported that boron fluoride, preferably mixed with some hydrogen fluoride, converted cyclohexene into di-, tri-, tetra- and higher polymers; the dimer was characterized by oxidation to the keto-acid II. Concentrated sulfuric acid was found by Nametkin[5] to convert cyclohexene at 5° to an oil (40%) which consisted of a *saturated*



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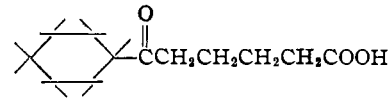

II

dimer and trimer, and an *unsaturated* tetramer. From the residue which remained after the distillation of this oil a tetracyclohexyl-cyclohexene, m. p. 83–85°, and a tetracyclohexyl-benzene, m. p. 265°, were isolated and identified. Aluminum chloride was reported[5] to give similar results.

Waterman, Leendertsa and ter Poorten[6] also studied the polymerization of cyclohexene with aluminum chloride; they found that this catalyst had no effect on the olefin at −78°, very little at 40°, but at 70° produced a considerable amount of polymers. These investigators made the interesting observation that a combination of aluminum chloride and hydrogen chloride caused polymerization of cyclohexene at −78° but that neither reagent alone had any effect on the olefin at this temperature, and, since they found that

(1) Harshaw Chemical Company Fellow, 1942–1944.

(2) *Cf.* McElvain and Langston, THIS JOURNAL, **65**, 2239 (1943), for the trimerization of ketene acetal with hydrogen fluoride.

(3) Truffault, *Bull. soc. chim.*, [5] **3**, 442 (1936); *Compt. rend.*, **200**, 406 (1935).

(4) Hofmann, *Chem. Ztg.*, **57**, 5 (1933).

(5) Nametkin, *et al.*, *Ber.*, **66**, 358 (1933); *J. Gen. Chem. Soc.* (U. S. S. R.), **7**, 759, 763 (1937), *Chem. Abst.*, **31**, 5750 (1937).

(6) Waterman, Leendertsa and ter Poorten, *Rec. trav. chim.*, **54**, 245 (1935).