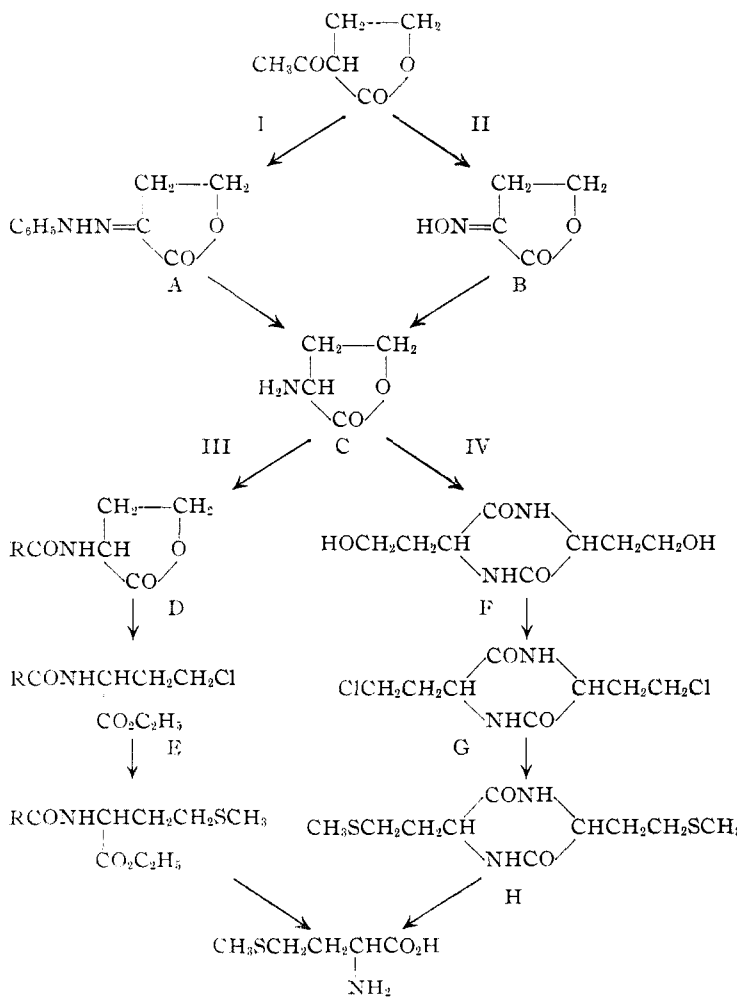
[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

A Convenient Synthesis of *dl*-Methionine

BY H. R. SNYDER, JOHN H. ANDREEN, GEORGE W. CANNON AND CARL F. PETERS

The synthesis of *dl*-methionine from the benzoyl derivative of α-amino-γ-butyrolactone, described by Hill and Robson,[1] does not require the use of the strongly vesicant β-chloroethylmethyl sulfide employed in the syntheses of Windus and Marvel[2] and of Barger and Weichselbaum.[3] However, α-amino-γ-butyrolactone has been difficult to prepare and consequently has not been much used in the preparation of methionine. Recently, certain derivatives of α-amino-γ-butyrolactone have been prepared from the easily available α-aceto-γ-butyrolactone.[4] Feofilaktov and Onishchenko[5] have obtained the hydrochloride of the aminolactone by reduction of α-oximino-γ-butyrolactone with tin and hydrochloric acid. They reduced the phenylhydrazone of α-keto-γ-butyrolactone in the same manner and obtained the hydrochloride of α-amino-γ-hydroxybutyric acid. The oxime and phenylhydrazone[6] were prepared by the action of nitrous acid and benzenediazonium chloride, respectively, on α-aceto-γ-butyrolactone.

The availability of α-amino-γ-butyrolactone from these reactions suggested a re-examination of the use of its acyl derivatives in the synthesis of *dl*-methionine. However, a possible route to *dl*-methionine involving the conversion of the aminolactone to 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine was considered more attractive. Fischer and Blumenthal[7] have observed that the aminolactone readily changes to the diketopiperazine. In the accompanying scheme path III (R = C_6H_5) represents the synthesis of Hill and Robson,[1] who employed α-aminobutyrolactone prepared by a more tedious method; path IV represents the projected synthesis by way of the diketopiperazine.



In the present study the phenylhydrazone of α-keto-γ-butyrolactone (A) was prepared by the method of Harradence and Lions[6] and was subjected to catalytic reduction. When the reduction was carried out in ethanol over Raney nickel, temperatures of 100–150° were required and the product was not the aminolactone (C) but the diketopiperazine (F). When the reduction was carried out in ethyl acetate containing acetic an-

(1) Hill and Robson, *Biochem. J.*, **30**, 246 (1936).

(2) Windus and Marvel, THIS JOURNAL, **52**, 2575 (1930).

(3) Barger and Weichselbaum, "Organic Syntheses," **XIV**, 58 (1934).

(4) Knunyantz, *Compt. rend. acad. sci.* (U. R. S. S.), N. S. **1**, 312 (1934).

(5) Feofilaktov and Onishchenko, *J. Gen. Chem.* (U. S. S. R.), **9**, 304, 314 (1939).

(6) Previously prepared by Harradence and Lions, *J. Proc. Royal Soc. N. S. Wales*, **72**, 221 (1938).

(7) Fischer and Blumenthal, *Ber.*, **40**, 111 (1907).

hydride, a mixture of acetanilide and α-acetamino-γ-butyrolactone (D, R = CH_3) was produced. It was possible to separate these by water extraction and distillation and thus to obtain α-acetamino-γ-butyrolactone in yields of about 30%. When this substance was treated with hydrogen chloride and ethanol according to the method of Hill and Robson[1] for the corresponding benzamino derivative, the acetyl group was removed and the hydrochloride of α-amino-γ-butyrolactone was produced; none of the desired ethyl α-acetamino-γ-chlorobutyrate (E) was isolated.

α-Oximino-γ-butyrolactone (B) was prepared from ethyl nitrite and α-aceto-γ-butyrolactone in methanol solution. The oxime was hydrogenated over either Raney nickel or palladium-charcoal in methanol or ethanol solution. The resulting solution, after removal of the catalyst, was heated under reflux for twenty-four hours to effect the conversion of α-amino-γ-butyrolactone (C) to the dihydroxydiketopiperazine (F). This substance was obtained from the oxime in yields of 55–60%. It was identical with the diastereoisomeric modification previously obtained by Fischer and Blumenthal.[7] It was converted to 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine (G), in yields of 90–95%, by treatment with excess thionyl chloride. 3,6-*bis*-(β-Methylthiolethyl)-2,5-diketopiperazine (H) was obtained in 63% yield from the reaction of the chloro derivative with sodium methylmercaptide. Hydrolysis of this diketopiperazine gave *dl*-methionine in 85–95% yield. These reactions constitute a convenient and economical method for the preparation of the amino acid.

Experimental

1. Hydrogenation of the Phenylhydrazone of α-Keto-γ-butyrolactone in Ethanol.—Acetobutyrolactone was prepared by the method of Knunyantz.[4] It was converted to the phenylhydrazone of α-keto-γ-butyrolactone by the procedure described by Harradence and Lions.[6] The crude phenylhydrazone was washed with water until the washings were free of halide ion, then dried and extracted with boiling ethanol or ethyl acetate to remove colored impurities. In one reduction 70 g. of the phenylhydrazone and 250 cc. of absolute ethanol were placed in a bomb with Raney nickel. Hydrogen under 1700 lb. pressure was admitted and the bomb was heated to 100° for four hours. During this period hydrogen was absorbed slowly, so the temperature was raised to 150° for eight hours. The ethanol was removed from the filtered solution by distillation under diminished pressure. The residue was a mixture of an oil (aniline) and a white solid (the diketopiperazine). The oil was removed by extraction with ether and the residual solid was crystallized from ethanol; it melted at 178–180°. The yield was 20 g. (54%). However, in other runs in which the temperature was kept constant at various temperatures between 100° and 150° the yield did not exceed 20%.

2. Hydrogenation of the Phenylhydrazone of α-Keto-γ-butyrolactone in the Presence of Acetic Anhydride.—A mixture of the phenylhydrazone (115 g.), acetic anhydride (170 cc.), and ethyl acetate (350 cc.) was placed in the bomb with Raney nickel and heated at 125° until hydrogen (initial pressure, 2000 lb.) was no longer absorbed. The solution contained nickel salts which were removed by treatment with hydrogen sulfide. The solvent was removed from the filtered solution by evaporation under 20 mm. pressure from a water-bath maintained at 90°. The residue was added to 500 cc. of cold water and the mixture was stirred rapidly and warmed to 40°. The aqueous solution was separated from the undissolved acetanilide (m. p. 113°) and evaporated to dryness under 20 mm. pressure. The sirupy residue was distilled and the fraction boiling at 175–178° (2 mm.) was collected as a pale yellow sirup which crystallized on standing; m. p. 82–84°. The yield was 29 g. or 30%.

Anal. Calcd. for $C_6H_9O_3N$: C, 50.35; H, 6.30; N, 9.79. Found: C, 50.43; H, 6.40; N, 9.72.

3. Reaction of α-Acetamino-γ-butyrolactone with Ethanol and Hydrogen Chloride.—The procedure of Hill and Robson[1] was used, except that an equivalent weight of α-acetamino-γ-butyrolactone was substituted for the benzamino derivative. The sirup remaining after evaporation of the ethanol was insoluble in ether. After crystallization from acetone it melted at 200–201° (lit.,[5] 201°) and analysis showed it to have the composition of α-amino-γ-butyrolactone hydrochloride; the yield was 40%.

4. Preparation of α-Oximino-γ-butyrolactone.—To a cold (0 to −5°) solution of 256 g. (2 moles) of acetobutyrolactone in 500 cc. of methanol was added 300 g. (4 moles) of ethyl nitrite prepared from hydrochloric acid, sodium nitrite and ethanol.[8] The reaction flask was packed in ice–salt and allowed to stand for fifteen to twenty hours, during which time the ice melted and the temperature of the reaction mixture reached that of the room. The mixture was cooled and the crystalline solid was collected on a filter. The filtrate was concentrated under diminished pressure and the dark-colored residue was heated on the steam-bath with 100 cc. of *n*-butyl alcohol. The mixture was cooled and filtered. The two crops of crystals were combined, washed twice with 100-cc. portions of cold *n*-butyl alcohol and then with ether. The α-oximino-γ-butyrolactone weighed 196–209 g. (85–91%) and melted at 183–185° (lit.,[5] 192°).

5. 3,6-*bis*-(β-Hydroxyethyl)-2,5-diketopiperazine.—Solutions of the oxime in methanol (about 4 cc. per g.) were hydrogenated over a palladium catalyst. The catalyst was prepared by evaporating to dryness a mixture of charcoal, previously washed with nitric acid, and aqueous palladium chloride. Quantities were chosen so that the dry catalyst contained the equivalent of 5% of metallic

(8) Evidently the reaction is catalyzed by a trace of hydrogen chloride, for reactions employing ethyl nitrite made from sulfuric acid have been found to proceed very slowly unless a small amount of an acid is added. For these observations the authors are indebted to Dr. E. E. Howe of Merck and Co., Inc., Rahway, N. J.

palladium. Two grams of the impregnated charcoal was used for each 100 cc. of methanol. The reductions were carried out at low pressure (50 lb. at start). They proceeded very rapidly (thirty minutes for a 25-g. run) and with the evolution of heat. When the hydrogen absorption was complete the catalyst was removed and the solution was heated under reflux for forty-eight hours, then stored in a refrigerator overnight. The crystalline solid was collected and washed with cold alcohol and cold ether; it melted at 186° with decomposition (lit.,[7] 189°). The yields were from 55–60%.

6. 3,6-*bis*-(β-Chloroethyl)-2,5-diketopiperazine.—The following procedure has given the best yields. In a 500-cc. flask fitted with a stirrer and reflux condenser 110 cc. of thionyl chloride was cooled to 0 to −5°, and 15 g. of 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine was added in one lot. The mixture was stirred and allowed to come to room temperature slowly. The flask was then immersed in a water-bath which was very slowly warmed until the thionyl chloride began to reflux. The mixture was cooled and diluted with 75 cc. of dry ether. The solid was collected on a filter and washed twice with ether, then twice with water. Drying of the product may be facilitated by washing with alcohol and ether. The dry product was a very light yellow or white solid of m. p. 230–231°; the yield was 15.8–17 g. (90–95%). The substance can be recrystallized from ethanol or acetic acid, but the amount of solvent required is large (about 50 cc. per g.) and the melting point is not changed.

Anal. Calcd. for $C_8H_{12}O_2N_2Cl_2$: N, 11.7. Found: N, 11.4.

Larger runs have been made in the same way, but there is danger of uncontrollable boiling of the thionyl chloride when the reaction sets in. Addition of thionyl chloride to the hydroxyl compound suspended in an inert solvent, such as chloroform, gave lower yields and the product was of a dark color. The use of thionyl chloride and pyridine resulted in very poor yields.

7. 3,6-*bis*-(β-Methylthiolethyl)-2,5-diketopiperazine.—The chloro compound was mixed with a solution containing a 10% excess of sodium methylmercaptide (2.2 moles per mole of chloro compound) in absolute ethanol. Absolute ethanol was added until the total volume was about three liters per mole of chloro compound. This mixture, in a flask provided with a reflux condenser, was heated cautiously on the steam-bath. As soon as the reaction began the steam was turned off. Refluxing continued for about ten minutes without external heating; when boiling subsided steam was again applied until the total period of reflux was one hour. The boiling solution was filtered through a heated funnel and the filtrate was cooled in ice-water. The crystals were collected and the mother liquor was used for a second hot extraction of the original residue. The total yield from three such extractions was 63%. The material could be freed of a yellow-colored impurity, which was sometimes present, by washing with water, and the white diketopiperazine so produced melted at 225–226°. It could be recrystallized from ethanol to yield a product melting at 231–232°, but the crude material is satisfactory for the next step.

Anal. Calcd. for $C_{10}H_{18}O_2N_2S_2$: C, 45.9; H, 6.9. Found: C, 46.0; H, 7.0.

8. *dl*-Methionine.—The 3,6-*bis*-(β-methylthiolethyl)-2,5-diketopiperazine was mixed with concentrated hydrochloric acid (15 cc. per g.). The clear solution which resulted when the mixture was warmed was heated under reflux for three hours. The solution was evaporated to dryness under diminished pressure and the residue was dissolved in boiling absolute ethanol (20 cc. per g. of diketopiperazine used). This solution was clarified with charcoal and, while still hot, was treated with pyridine (1–2 cc. per g. of diketopiperazine) until an excess was present. Crystallization of *dl*-methionine began immediately. The mixture was allowed to stand in a refrigerator (0–5°) overnight and the product was collected, washed with cold absolute alcohol and then with absolute ether. The yield of *dl*-methionine was 85–95%.

Summary

A convenient and economical synthesis of *dl*-methionine is described. α-Aceto-γ-butyrolactone is converted to α-oximino-γ-butyrolactone by treatment with ethyl nitrite in the presence of a trace of mineral acid; the α-oximino-γ-butyrolactone is reduced catalytically to α-amino-γ-butyrolactone which changes to 3,6-*bis*-(β-hydroxyethyl)-2,5-diketopiperazine; 3,6-*bis*-(β-chloroethyl)-2,5-diketopiperazine is prepared by the action of thionyl chloride on the corresponding hydroxy compound and is converted to the anhydride of methionine by treatment with sodium methylmercaptide; *dl*-methionine is obtained by acid hydrolysis of the anhydride.

URBANA, ILLINOIS RECEIVED JUNE 29, 1942