200 cc. of ether and filtered to remove the suspended catalyst. The ether solution was washed repeatedly with dilute hydrochloric acid, with dilute sodium hydroxide, and with water. Removal of ether left an oil which distilled at 108–115° under a pressure of 12 mm. The yield was 5.9 g., 58% of the theoretical. This material gave no color with ferric chloride in aqueous ethanol.

Dibenzoate of 3,4-Dioxythiophene (VI).—All operations were performed under an atmosphere of nitrogen to reduce oxidation of the intermediate 3,4-dioxythiophene. A solution of 0.8 g. of 3,4-dimethoxythiophene (III) in 5 cc. of dry benzene was heated for twenty minutes at 60° with 1.6 g. of anhydrous aluminum chloride. The resulting dark-colored suspension was poured onto ice and dilute hydrochloric acid. The acid solution was extracted with ether and the hydroxythiophene was extracted from the ether–benzene solution with sodium hydroxide. Treatment of the alkaline solution with a slight excess of benzoyl chloride gave VI. The dibenzoate was crystallized from dilute ethanol; m. p. 109.5–110°. This compound gives no color with aqueous ferric chloride.

Anal. Calcd. for $C_{18}H_{12}O_4S$: S, 9.88. Found: S, 9.94.

(3,4-Dimethoxy Thienoyl)-propionic Acid (IV).—A solution of 12.45 g. of 3,4-dimethoxythiophene (III) in 200 cc. of dry thiophene-free benzene was cooled to 5° under an atmosphere of nitrogen. A solution of 13 g. of $CH_3OCO-CH_2CH_2COCl$ and 10.15 cc. of anhydrous stannic chloride in 75 cc. of dry thiophene-free benzene was added dropwise to the stirred solution of the thiophene. After one and one-half hour's stirring at 5°, the material was poured onto ice and dilute hydrochloric acid. The benzene layer was separated and the water layer was extracted several times with ether. After removal of the solvents, a small amount of volatile side product was removed by heating to 150° under a pressure of 1 mm. The resulting residue was refluxed with 20 cc. of 6 *N* sodium hydroxide. After the alkaline solution had been extracted with ether to remove a small amount of alkali-insoluble oil, it was added dropwise to 20 cc. of 6 *N* hydrochloric acid. The cream-colored precipitate weighed 10.67 g. This is 50.5% of the theoretical yield based on the weight of 3,4-dimethoxythiophene used. Crystallization from water gave white needles; m. p. 134.5–135.5°. This compound gives no color with ferric chloride in aqueous ethanol.

Anal. Calcd. for $C_{10}H_{12}O_5S$: C, 49.20; H, 4.92; S, 13.12; neut. equiv., 244. Found: C, 48.77; H, 4.71; S, 12.92; neut. equiv., 244, 246.

Summary

Some derivatives of 3,4-dioxythiophene have been prepared during investigation of methods of synthesis of compounds structurally related to biotin.

NEW HAVEN, CONNECTICUT
RECEIVED SEPTEMBER 15, 1945

[CONTRIBUTION FROM THE ORGANIC RESEARCH LABORATORY OF THE DOW CHEMICAL COMPANY]

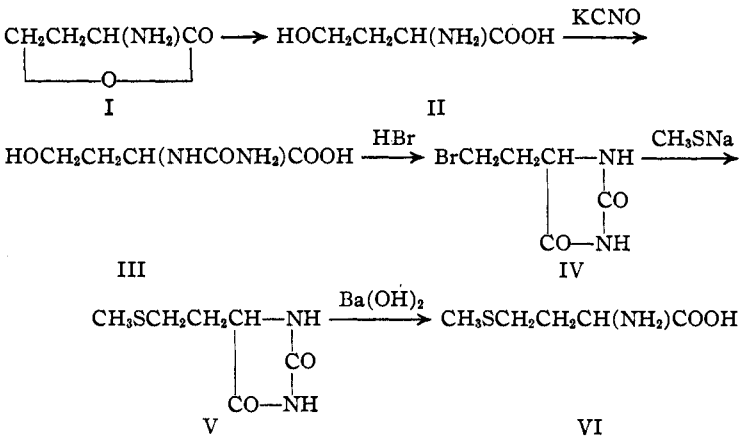
Synthesis of *dl*-Methionine

BY J. E. LIVAK, E. C. BRITTON, J. C. VANDERWEELE AND M. F. MURRAY

The recently described syntheses of methionine by Booth, Burnop and Jones[1] and by Albertson and Tullar[2] suffer from the disadvantage of employing the strong vesicant β-chloroethylmethyl sulfide. The method of Hill and Robson,[3] employing α-amino-γ-butyrolactone, and the later modification reported by Snyder and co-workers,[4,5] are excellent laboratory procedures but possess certain operational disadvantages. It has now been found that the convenient synthesis of *dl*-methionine on a large scale can be realized by utilization of the readily available γ-butyrolactone.[6] Bromination of γ-butyrolactone gives α,γ-dibromobutyric acid which, on distillation or treatment with cold alkali, loses hydrogen bromide to give α-bromo-γ-butyrolactone in good yield. The chlorination of γ-butyrolactone was also studied but it was found that conversion of the α,γ-dichlorobutyric acid to γ-chlorobutyrolactone was not as convenient as through the brominated derivatives. Elaboration on the chemistry of these halogenated lactones and acids will be the subject of a separate paper. Amination of the α-bromo-γ-butyrolactone easily gives α-amino-γ-butyrolactone, from which compound the synthesis of methionine can be realized by three different procedures: (1) by the benzoylation method of Hill and Robson,[3] (2) by the diketopiperazine method of Snyder and co-workers[4] and (3) by the sequence of reactions shown.

Because of the unstable nature of α-amino-γ-butyrolactone (I), described by Fischer and Blumenthal[7] as a colorless sirup, it was not isolated in the present work but was converted to crystalline derivatives. The product obtained in the amination of α-bromo-γ-butyrolactone was either isolated as α-amino-γ-hydroxybutyric acid (II) or treated with aqueous hydrobromic acid solution to give α-amino-γ-butyrolactone hydrobromide. Conversion of the hydrobromide to 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine[4,7] was effected by treatment with potassium acetate in alcohol solution, removal of potassium bromide by filtration and heating of the filtrate under reflux to effect conversion of the α-amino-γ-butyrolactone to 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine. Other neutralization agents, including sodium acetate, sodium formate and sodium methylate were used, but the yields of the diketopiperazine were consistently lower than those obtained with potassium acetate. An attempt to prepare the diketopiperazine directly from α-amino-γ-hydroxybutyric acid proved unsuccessful.

(1) Booth, Burnop and Jones, *J. Chem. Soc.*, 666–667 (1944).
(2) Albertson and Tullar, THIS JOURNAL, **67**, 502 (1945).
(3) Hill and Robson, *Biochem. J.*, **30**, 248 (1936).
(4) Snyder, Andreen, Cannon and Peters, THIS JOURNAL, **64**, 2082 (1942).
(5) Snyder and Cannon, *ibid.*, **66**, 511 (1944).
(6) The γ-butyrolactone was obtained from the Cliffs Dow Chemical Company.
(7) Fischer and Blumenthal, *Ber.*, **40**, 11 (1907).



For the conversion of α-amino-γ-hydroxybutyric acid to methionine the compound was treated with potassium cyanate in water solution. The reaction mixture was then treated with aqueous hydrobromic acid to effect simultaneous ring closure of the α-ureido acid (III) and replacement of the hydroxyl group by bromine. The yield of 5-(β-bromoethyl)-hydantoin (IV) by this procedure was approximately 50%. Condensation of 5-(β-bromoethyl)-hydantoin with sodium methylmercaptide gave 5-(β-methylmercaptoethyl)-hydantoin (V), which on hydrolysis with barium hydroxide solution gave *dl*-methionine (VI) in 95% yield.

An alternate procedure for the synthesis of 5-(β-bromoethyl)-hydantoin in excellent yield involves the opening of the alicyclic ring of 5-cyclopropanespirohydantoin[8] with concentrated hydrobromic acid solution.

Experimental

α-Bromobutyrolactone.—A mixture of 1120 g. (13.0 moles) of γ-butyrolactone and 25 cc. of phosphorus tribromide contained in a two-liter round-bottom flask fitted with a seal stirrer, reflux condenser, thermometer and a dropping funnel dipping below the surface, was heated to 100° and 1975 g. (12.35 moles) of bromine added at 100–130° over a period of ten hours. After heating for an additional four hours at 130°, the bromination mixture was distilled *in vacuo*, the hydrogen bromide evolved being absorbed in caustic. In addition to 108 g. of low boiling material, there was obtained 2100 g. of product, b. p. 120–140° at 7 mm. The crude material was redistilled in an efficient still to yield 1675 g. of α-bromo-γ-butyrolactone, b. p. 130–131° at 8 mm., d^{25} 1.79, $n^{25}D$ 1.5094; yield 82%.

Anal. Calcd. for $C_4H_5BrO_2$: Br, 48.48. Found: Br, 49.76.

α-Amino-γ-butyrolactone Hydrobromide.—α-Bromo-γ-butyrolactone (115.5 g.; 0.7 mole) was added with good stirring and ice cooling to 216 cc. (3.7 moles) of 32% ammonium hydroxide at a temperature not exceeding 25°. The intensely red solution was allowed to stand overnight, diluted with water to 700 cc., and 280 cc. of 2.5 *N* potassium hydroxide solution was added. After atmospheric distillation of the ammonia, the residual solution was evaporated to dryness under water pump vacuum. The semicrystalline residue was digested with a solution of 92 g. (0.6 mole) of 53% hydrobromic acid solution in 630 cc. of ethanol and 70 cc. of water on the steam-bath at 70° for one-half hour. After cooling, the potassium bromide was collected on a suction filter and the filtrate was distilled at atmospheric pressure to remove the alcohol and then evaporated to dryness under water pump vacuum. The light tan crystalline residue was digested with 500 cc. of methanol at 65°, cooled, and a second crop of potassium bromide removed by filtration. Methanol was distilled from the filtrate and it was concentrated *in vacuo*. The heavy sirup was treated with 100 cc. of 53% hydrobromic acid solution on the steam-bath for one hour. The clear solution was evaporated at 10 mm. pressure to dryness, the semicrystalline residue digested with 200 cc. of hot absolute ethanol, the mixture cooled and the product collected on a suction filter. The weight of α-aminobutyrolactone hydrobromide was 59.5 g. Evaporation of the filtrate to dryness and treatment with 48% hydrobromic acid solution gave an additional 5.2 g. of compound; yield 59.3%. The compound sintered at 215° and melted at 221° with decomposition (lit.[7] 217°, 227°).

Anal. Calcd. for $C_4H_8BrNO_2$; Br, 43.92; N, 7.70. Found: Br, 44.60; N (Kjeldahl), 7.25.

3,6-Bis-(β-hydroxyethyl)-2,5-diketopiperazine.—To a solution of 9.8 g. (0.1 mole) of potassium acetate in 150 cc. of absolute ethanol at 50° was added 16.7 g. (0.09 mole) of powdered α-amino-γ-butyrolactone hydrobromide. The resultant slurry was heated to 75° with good shaking, cooled to 50° and the potassium bromide filtered off and washed with absolute ethanol. The filtrate was heated under reflux for four hours to yield, on cooling, 5.2 g. of 3,6-bis-(β-hydroxyethyl)-2,5-diketopiperazine, m. p. 188–189° (dec.). An additional 1.6 g. of compound, m. p. 187–189°, was obtained from the mother liquor; yield 73%.

α-Amino-γ-hydroxybutyric Acid, II.—α-Bromo-γ-butyrolactone (165 g.; 1.0 mole) was added with good stirring to 990 cc. (15.0 moles) of 28% ammonium hydroxide solution and the mixture allowed to stand at room temperature for two days. After evaporation to a volume of 300 cc., the clear solution was treated with lead oxide on the steam-bath until a filtered sample failed to give a test for bromide. The filtered solution was treated with hydrogen sulfide, the lead sulfide removed by suction filtration and the clarified solution evaporated to dryness under reduced pressure. The viscous sirup was digested with 300 cc. of hot methanol, cooled and the α-amino-γ-hydroxybutyric acid filtered off and washed well with cold methanol; weight 43 g.; yield 36%.

The methanol mother liquor, after evaporation to dryness, was treated with aqueous hydrobromic acid solution to yield 36.5 g. of α-amino-γ-butyrolactone hydrobromide.

5-(β-Bromoethyl)-hydantoin, IV.—A solution of 13 g. (0.16 mole) of potassium cyanate in 25 cc. of water was added to a solution of 17.9 g. (0.15 mole) of α-amino-γ-hydroxybutyric acid in 75 cc. of water. The mixture was heated with stirring at 65° for two hours, cooled, and the solution of γ-hydroxy-α-ureidobutyric acid (not isolated) was treated with 100 cc. of 48% hydrobromic acid. After heating at 90° for two hours, the dark solution was evaporated to dryness at 15 mm. pressure. The semicrystalline residue was digested with 150 cc. of hot acetone and the potassium bromide removed by filtration. The acetone was evaporated and the residue treated with 100 cc. of 48% hydrobromic acid, heated for two hours at 90° and the hydrobromic acid distilled off under vacuum. The residual dark gel was dissolved in 100 cc. of hot water to give, on cooling, 19 g. of light tan product. Recrystallization from water gave 16 g. of 5-(β-bromoethyl)-hydantoin, m. p. 141.5–142°; yield 51.5%.

Anal. Calcd. for $C_5H_7BrN_2O_2$: Br, 38.68; N, 13.53. Found: Br, 38.46; N, 12.52.

5-(β-Bromoethyl)-hydantoin (from 5-Cyclopropanespirohydantoin).—A mixture of 5 g. (0.04 mole) of 5-cyclo-

(8) Ingold, Sako and Thorpe, *J. Chem. Soc.*, **121**, 1190 (1922).

propanespirohydantoin (prepared according to the procedure of Ingold, Sako and Thorpe[8]) and 15 cc. of 66% hydrobromic acid was heated in an oil-bath at 120° for one hour. After removal of the hydrobromic acid by distillation at 20 mm. the solid residue was recrystallized from ethanol. The total weight of 5-(β-bromoethyl)-hydantoin was 7.3 g., m. p. 141–142°; yield 87%.

5-(β-Methylmercaptoethyl)-hydantoin, V.—To a solution of 10.35 g. (0.05 mole) of 5-(β-bromoethyl)-hydantoin in 75 cc. of absolute ethanol was added a solution of sodium methylmercaptide (prepared by bubbling 2.5 g. (0.05 mole) of methyl mercaptan[9] from a cylinder into a solution of 2.8 g. (0.05 mole) of sodium methylate in 50 cc. of absolute ethanol. The mixture was heated under reflux for one hour, most of the alcohol removed by evaporation, and the residue diluted with water. Acidification to the neutral point with 6 *N* hydrochloric acid gave a copious precipitate, which after recrystallization from water melted at 105–106° (lit.[3], 117°); weight 6.4 g.; yield 73.5%.

Anal. Calcd. for $C_6H_{10}N_2O_2S$: N, 16.09; S, 18.39. Found: N, 15.11; S, 18.81.

***dl*-Methionine, VI.**—A mixture of 17.4 g. (0.1 mole) of 5-(β-methylmercaptoethyl)-hydantoin, 50.5 g. (0.16 mole) of barium hydroxide octahydrate and 300 cc. of water was charged into a 450-cc. rotating iron autoclave and heated at 155° for fifteen minutes. After removal of the barium carbonate, the filtrate was shaken with 9.1 g. (0.08 mole) of ammonium carbonate monohydrate, the barium carbonate removed by filtration and the filtrate evaporated under water pump vacuum to dryness. The residue was slurried with ethanol and suction filtered to yield 14.2 g. of *dl*-methionine; m. p. 268–270° (dec.); yield 95%.

Anal. Calcd. for $C_5H_{11}NO_2S$: N, 9.40; S, 21.48. Found: N, 9.30; S, 21.41.

(9) Pure methyl mercaptan is commercially available from the Union Oil Company.

Summary

A convenient synthesis of *dl*-methionine is described. γ-Butyrolactone is brominated, the α-bromo-γ-butyrolactone thus obtained is aminated to yield α-amino-γ-hydroxybutyric acid, which, with potassium cyanate, gives γ-hydroxy-α-ureidobutyric acid. Treatment of the ureido acid with concentrated hydrobromic acid gives 5-(β-bromoethyl)-hydantoin, which, with sodium methylmercaptide, is converted to 5-(β-methylmercaptoethyl)-hydantoin, from which *dl*-methionine is obtained by alkaline hydrolysis.

MIDLAND, MICH. RECEIVED AUGUST 13, 1945

[CONTRIBUTION FROM SOUTHERN REGIONAL RESEARCH LABORATORY, NEW ORLEANS, LOUISIANA[1]]

The Organic Acid Content of Raw Cotton Fiber. Isolation of *l*-Malic Acid and Citric Acid from Cotton Fiber

BY ELIZABETH R. McCALL AND JOHN D. GUTHRIE

A typical sample of oven-dry raw cotton fiber contains about 94% cellulose, 1.3% protein, 1.2% pectic substances, 1.2% ash, 0.6% wax and 0.3% sugars.[2] Even on this crude basis, about 1.4% of the fiber is unaccounted for. A consideration of some of the properties of raw cotton fiber, especially its high content of alkaline ash, indicates that it probably contains considerable quantities of the organic acids commonly found in plants. These acids probably occur in the fiber as potassium, calcium, magnesium and sodium salts. Four samples of raw cotton fiber were analyzed for malic acid, citric acid, oxalic acid and total organic acids. Since these analyses showed about 0.5% malic acid and 0.07% citric acid, it seemed feasible to isolate these acids from raw cotton fiber and thus remove any doubt as to their occurrence in the fiber.

Experimental

Description of Samples.—The following samples of cleaned raw cotton roving were analyzed:

Sample No. 1. Variety: Unknown. Source: U. S. Dry Land Field Station, Big Springs, Texas. Grade: Strict low middling. Staple: 1 inch.
Sample No. 2. Variety: Wilds. Grade: Strict middling. Staple: $1^5/_{16}$ inch.
Sample No. 3. Variety: Stoneville. Grade: Middling. Staple: $1^3/_{32}$ inch.
Sample No. 4. Variety: SXP. Staple: $1^1/_2$ inch.

Analysis of Raw Cotton for Organic Acids.—Samples weighing about 20 g. were placed in desiccators over concentrated hydrochloric acid for forty-eight hours and extracted in Soxhlet extractors for forty-eight hours with ethyl ether purified according to Pucher and Vickery.[3] The ether extracts were neutralized with 5 *N* sodium hydroxide solution free of carbonates, transferred to 100-ml. volumetric flasks, made to volume with carbon dioxide-free water and filtered through dry filter paper. Aliquots of the filtrate were analyzed for malic acid, citric acid, oxalic acid and total organic acids by the methods of Pucher, Wakeman and Vickery.[4] All determinations were made in duplicate but averages are reported in Table I.

TABLE I

ORGANIC ACID CONTENT OF RAW COTTON FIBER IN PER CENT. OF THE DRY WEIGHT

Sample no.	Malic acid	Citric acid	Oxalic acid	Unidentified organic acids[a]	Total organic acids[a]
1	0.49	0.05	0.004	0.33	0.87
2	.57	.10	.005	.24	.91
3	.48	.07	.005	.27	.82
4	.32	.05	.002	.40	.77

[a] Calculated in terms of an acid with an equivalent weight of 67.

(1) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

(2) John D. Guthrie, Carroll L. Hoffpauir, Edward T. Steiner and Mack F. Stansbury, Mimeographed Circular AIC-61 (1944), Bureau of Agricultural and Industrial Chemistry.

(3) G. W. Pucher, H. B. Vickery and A. J. Wakeman, *Ind. Eng. Chem., Anal. Ed.*, **6**, 140–143 (1934).

(4) (a) G. W. Pucher, *J. Biol. Chem.*, **153**, 133–137 (1944); (b) G. W. Pucher, A. J. Wakeman and H. B. Vickery, *Ind. Eng. Chem., Anal. Ed.*, **13**, 244–246 (1941).