[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY]

Synthesis of α-Amino-γ-halogenobutyric Acids. A New Synthesis of DL-Homoserine

BY MAX FRANKEL AND Y. KNOBLER[1]

RECEIVED DECEMBER 9, 1957

New syntheses of α-amino-γ-halogenobutyric acids and of DL-homoserine are given. Conditions for the opening of the free and the N-substituted α-amino-γ-butyrolactone to the respective γ-halogeno compounds by aqueous hydrohalic acids were studied.

In the course of our investigations on trifunctional α-aminobutyric acids we have worked out new syntheses of α-amino-γ-halogenobutyric acids and of DL-homoserine[2] (α-amino-γ-hydroxybutyric acid). The convenient synthesis of the latter is based on the use of α-amino-γ-iodobutyric acid hydroiodide (II). This substance is prepared in 70% yield by amination of α-bromo-γ-butyrolactone[3] (I) and subsequent opening of the intermediate α-amino-γ-butyrolactone by prolonged heating with constant boiling hydroiodic acid. Heating of α-amino-γ-iodobutyric acid hydroiodide (II) with sodium hydroxide gave a mixture of crude homoserine and sodium iodide, from which pure DL-homoserine was obtained in 70% yield.

Treatment of the free α-amino-γ-iodobutyric acid, or its hydroiodide II as well as of the α-amino-γ-butyrolactone hydroiodide (IV) with silver carbonate and hydrogen sulfide also led to the DL-homoserine.

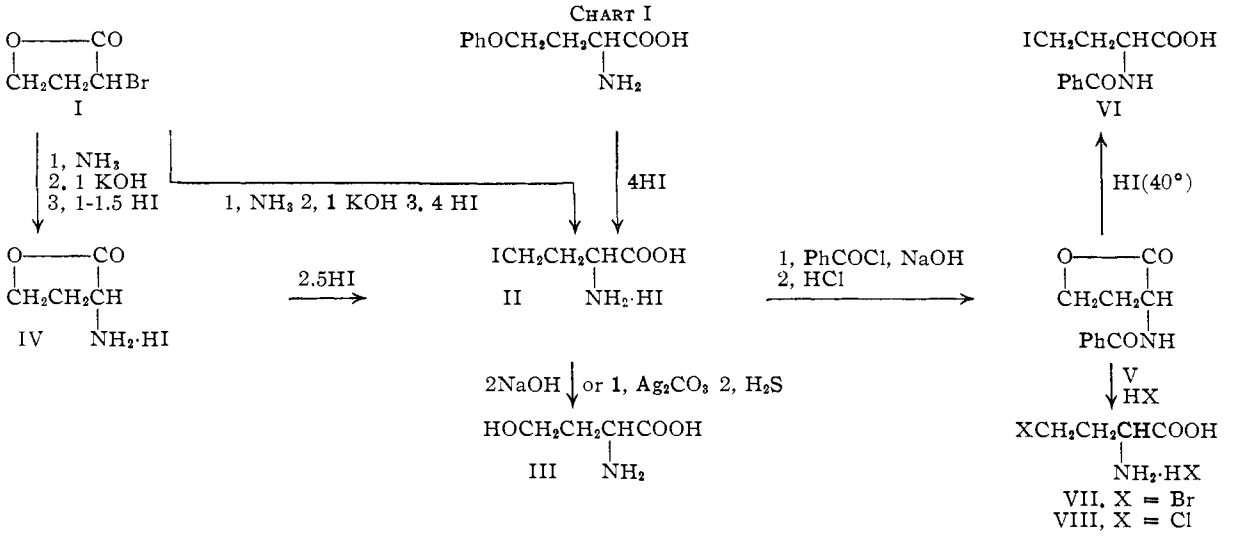
N-Acylated lactone derivatives, *e.g.*, N-carbobenzoxy- or N-benzoyl- DL-homoserine, can be prepared in good yield by direct treatment of the intermediate α-amino-γ-iodobutyric acid hydroiodide (II) with carbobenzoxy or benzoyl chloride.

α-Amino-γ-iodobutyric acid hydroiodide (II) also was obtained by cleavage of α-amino-γ-phenoxybutyric acid[2,4] with an excess of constant boiling hydroiodic acid. In this preparation too, the α-amino-γ-butyrolactone hydroiodide (IV) was the preceding intermediate and pure γ-iodo acid hydroiodide II could be obtained after prolonged refluxing with a great excess of constant boiling hydroiodic acid.

Treatment of α-benzamido-γ-butyrolactone (V) with constant boiling hydroiodic acid at 40° resulted in α-benzamido-γ-iodobutyric acid (VI).

The chloro and bromo analogs of α-amino-γ-iodobutyric acid hydroiodide (II) could not be produced from α-amino-γ-butyrolactone by treatment with the respective hydrohalic acids in a similar manner to that which led to the acid hydroiodide II. However, by prior benzoylation of the α-amino-γ-butyrolactone, the tendency for opening of the lactone ring with simultaneous γ-halogenation was greatly enhanced. Heating of α-benzamido-γ-butyrolactone (V) with 65% hydrobromic (40% hydrochloric) acid in a closed tube at 100° for seven hours gave α-amino-γ-bromo(chloro)-butyric acid hydrobromide[5a,b] (hydrochloride) (VII) (VIII) in 70% yield.

CHART I



The three α-amino-γ-halogenobutyric acid hydrohalogenides (II, VII, VIII) were esterified by the Fischer method to the respective methyl ester hydrochlorides.

Experimental

Micro-combustion analyses were made by Drs. Weiler and Strauss. Melting points were determined in a Fisher-Johns apparatus. The ascending method of paper-chromatography was used (80% phenol).

α-Amino-γ-iodobutyric Acid Hydroiodide (II).—82.5 g. (0.5 mole) of α-bromo-γ-butyrolactone (I) was added to 350 ml. of 25% ammonium hydroxide with cooling and

(1) Part of the thesis submitted to The Hebrew University in partial fulfillment of the requirements for the Ph.D. degree.

(2) E. Fischer and H. Blumenthal, *Ber.*, **40**, 106 (1907).

(3) J. E. Livak, THIS JOURNAL, **67**, 2218 (1945).

(4) E. P. Painter, *ibid.*, **69**, 232 (1947).

(5) (a) J. M. Gulland and C. J. O. R. Morris, *J. Chem. Soc.*, 763 (1935); (b) J. Baddiley and G. A. Jamieson, *ibid.*, 4280 (1954).

shaking and the stoppered solution allowed to stand for five days; 500 ml of *N* potassium hydroxide was added, the solution heated with stirring at 100° for one hour and ammonium hydroxide removed. The solution was then concentrated to sirupy consistency and 350 ml. of ethanol was added, then 69 ml. (0.5 mole) of constant boiling (c.b.) hydroiodic acid. The mixture was warmed to 40–50° for one-half hour, cooled, filtered from potassium bromide, the filtrate concentrated *in vacuo*, cooled and the second crop of potassium bromide filtered off. To the filtrate, 400 ml. of absolute ethanol was added and the solution concentrated *in vacuo;* successive further crops of potassium bromide were removed by filtrations. Sometimes a third portion of about 200–300 ml. of absolute ethanol (dried over magnesium ethoxide) had to be used to separate the rest of potassium bromide with concentration *in vacuo*. This also could be effected by digestion with acetone.

After entire removal of the potassium bromide, the filtrate was evaporated *in vacuo* to a heavy sirup which was dissolved in 206 ml. (1.5 moles) of c.b. hydroiodic acid; 200 ml. of toluene was added and the mixture refluxed for a period of six hours. It was then stirred vigorously and hydroiodic acid removed by azeotropic distillation. After cooling, toluene was removed by decantation and the remaining dark mass triturated with boiling chloroform for one-half hour. The mixture was cooled, the chloroform removed by decantation and the residue purified by extraction with dry ether in a Soxhlet apparatus until a white-yellowish granular product was obtained, m.p. 185–190°. The latter contained still a very small amount of potassium salt, but could be used directly for most of the following operations; yield 125 g. (70%).

Further purification could be effected by dissolving the substance in a small amount of acetone, filtering and precipitating with excess of ether. A white-yellowish crystalline material was obtained by solution in absolute ethanol (dried over magnesium ethoxide) and addition of a large excess of ether. The hydroiodide II separated out during prolonged standing, m.p. 195–200° dec.

Anal. Calcd. for $C_4H_9NO_2I_2$: C, 13.4; H, 2.5; N, 3.9. I, 71.1. Found: C, 13.4; H, 2.4; N, 4.0; I, 71.4.

The α-amino-γ-iodobutyric acid hydroiodide (II) is soluble in water, alcohol, acetone; insoluble in ether and petroleum ether. It is stable in concentrated hydroiodic acid from which it could be recovered quantitatively. From a solution of II dissolved in a small amount of water and allowed to stand for two hours at a temperature not exceeding 20°, the acid hydroiodide II could be recovered. *Anal.* Calcd.: N, 3.9; I, 71.1. Found: N, 3.9; I, 71.0. From a second sample dissolved in cold water and maintained at 0° for 24 hours, acid hydroiodide II also was recovered. *Anal.* Calcd.: N, 3.9; I, 71.1. Found: N, 3.9; I, 71.0. From a solution in water, heated to 50–60° for two hours or to boiling for one hour, only α-amino-γ-butyrolactone hydroiodide (IV) resulted. *Anal.* Calcd.: N, 6.1; I, 55.4. Found: N, 6.0; I, 56.0. Similarly, α-amino-γ-iodobutyric acid hydroiodide (II) was converted to α-amino-γ-butyrolactone hydroiodide (IV) by prolonged standing in dilute aqueous or acidic solution, in moist alcoholic solution, or by heating near the melting point.

α-Amino-γ-butyrolactone Hydroiodide (IV).—α-Bromo-γ-butyrolactone (I) (16.5 g., 0.1 mole) was aminated and treated as described for the acid hydroiodide II, adding only 7 ml. excess of c.b. hydroiodic acid after removal of the inorganic salt. Water and hydroiodic acid were removed also here by azeotropic distillation with toluene and the crude product purified by continuous ether extraction in a Soxhlet apparatus; yield 17.1 g. (75%), m.p. 175–180° dec.

Anal. Calcd. for $C_4H_6NO_2I$: C, 21.0; H, 3.5; N, 6.1; I, 55.4. Found: C, 20.3; H, 3.5; N, 6.1; I, 56.3.

By a similar treatment of α-amino-γ-hydroxybutyric acid with an excess of 0.5 mole of c.b. hydroiodic acid, or by refluxing only for one hour with a greater excess of c.b. hydroiodic acid, α-amino-γ-butyrolactone hydroiodide (IV) was obtained. Mixtures of the hydroiodide of the lactone IV and the acid II resulted on using an excess of 1–2 moles of c.b. hydroiodic acid. With an excess of 3 moles of c.b. hydroiodic acid pure α-amino-γ-iodobutyric acid hydroiodide (II) could be obtained in almost quantitative yield.

α-Amino-γ-iodobutyric Acid.—α-Amino-γ-iodobutyric acid hydroiodide (II) (17.85 g., 0.05 mole) was dissolved in 150 ml. of absolute ethanol (dried over magnesium ethoxide) and the solution was cooled to 0°; 5.6 g. (0.056 mole) of triethylamine was added and the cloudy solution was kept in a refrigerator for two days until complete precipitation and crystallization. The precipitate was filtered with suction, dried over phosphorus pentoxide, washed several times with dry ether, and dried again over phosphorus pentoxide; m.p. 183–185°, yield 9.2 g. (80%). Omission of washing gave a product melting at 95–105°, solidifying and melting again at 183–185°.

Anal. Calcd. for $C_4H_8NO_2I$: C, 21.0; H, 3.5; N, 6.1; I, 55.4. Found: C, 20.8; H, 3.6; N, 6.1; I, 55.0.

DL-Homoserine α-Amino-γ-hydroxybutyric Acid (III).—To a solution of 17.85 g. (0.05 mole) of α-amino-γ-iodobutyric acid hydroiodide (II) in 150 ml. of water was added 4.2 g. (0.105 mole) of sodium hydroxide in 50 ml. of water. The solution was concentrated to dryness on a steam-bath. Most of the sodium iodide was removed by extraction with acetone in a Soxhlet apparatus during 3–4 hours. The crude product was dissolved in little water and 15–20 ml. of ethanol was added followed by an excess of acetone (or ether). The mixture was kept for some days in a refrigerator to complete precipitation and crystallization. DL-Homoserine was filtered off and washed with small portions of absolute ethanol–acetone (1:5) and of ether; yield 4.2 g. (70%); based on α-bromo-γ-butyrolactone (I) 49%; m.p. 182°. Ascending paper chromatography gave an R_f value of 0.66.

Anal. Calcd. for $C_4H_9NO_3$: C, 40.3; H, 7.6; N, 11.76. Found: C, 40.0; H, 7.6; N, 11.5.

Preparations Using the Fischer[1] Method.—(a) To a solution of 8.92 g. (0.025 mole) of α-amino-γ-iodobutyric acid hydroiodide (II) in 150 ml. of water was added 7.6 g. (2.2 equiv.) of silver carbonate. The suspension was stirred and allowed to stand until the silver iodide separated out. The supernatant solution was treated with hydrogen sulfide, filtered and concentrated on a steam-bath to 5–10 ml. Some water was added, and the concentrated solution decolorized with Norit. To the filtrate was added 10–15 ml. of absolute ethanol followed by an excess of acetone (or ether) and the mixture kept in refrigerator until complete solidification and crystallization. The crystals were washed with small portions of (1:5) ethanol–ether; yield of pure DL-homoserine 2.15 g. (72%); based on α-bromo-γ-butyrolactone (I) 50%; m.p. 182°; R_f value 0.66.

Anal. Calcd. for $C_4H_9NO_3$: N, 11.76. Found: N, 11.5.

(b) α-Amino-γ-butyrolactone hydroiodide (IV) (5.73 g., 0.025 mole) was dissolved in water and treated with 3.8 g. (1.1 equiv.) of silver carbonate, subsequently with hydrogen sulfide and worked up as described under (a); yield 1.6 g. (54%); based on α-bromo-γ-butyrolactone (I), 40%; m.p. 182°; R_f value 0.66.

Anal. Calcd. for $C_4H_9NO_3$: N, 11.76. Found: N, 11.6.

(c) α-Amino-γ-iodobutyric acid (5.73 g., 0.025 mole) was dissolved in water and treated with 3.8 g. (1.1 equiv.) of silver carbonate, subsequently with hydrogen sulfide and worked up as described under (a); yield 2.1 g. (71%); based on α-bromo-γ-butyrolactone (I), 40%; m.p. 183°; R_f value 0.66.

Anal. Calcd. for $C_4H_9NO_3$: N, 11.76. Found: N, 11.6.

α-Benzamido-γ-butyrolactone (V).—Twenty grams (0.056 mole) of α-amino-γ-iodobutyric acid hydroiodide was dissolved in 400 ml. of 0.5 *N* sodium hydroxide, the solution cooled to 0° and 250 ml. (0.5 mole) of 2 *N* sodium hydroxide and 24 g. (0.16 mole) of benzoyl chloride was added with stirring simultaneously in small portions. After all the benzoyl chloride was added, the mixture was stirred for one hour with cooling and for a further hour without cooling. The filtered solution was diluted with 200 ml. of water, cooled, stirred and acidified with 18% hydrochloric acid. The stirred mixture, which contained a white foamy precipitate containing benzoic acid, α-benzamido-γ-hydroxybutyric acid and α-benzamido-γ-butyrolactone, was heated (80°) for one hour, allowed to cool to room temperature and finally in a bath of ice-water until complete crystallization. The precipitate was filtered and washed several times with ether to extract the benzoic acid. The remaining product melted at 139–140°, recrystallized from water m.p. 141–142°. The mother liquor was extracted with ether and the aqueous layer concentrated on a steam-bath, cooled and further quantities of α-benzamido-γ-butyrolactone were obtained; yield 9.8 g. (85%).

Anal. Calcd. for $C_{11}H_{11}NO_3$: N, 6.85. Found: N, 6.85.

α-Carbobenzoxyamino-γ-butyrolactone.—Forty-three grams (0.12 mole) of α-amino-γ-iodobutyric acid hydroiodide (II) was dissolved in 600 ml. of water and 200 ml. of pyridine. The solution was cooled to 0°, stirred rapidly and 24 g. (0.14 mole) of carbobenzoxy chloride was added dropwise during two hours. Stirring was continued for 0.5 hour with cooling and for further two hours without cooling. A semi-crystalline product precipitated which, after heating in water, solidified during standing in ice-water. After collection on a suction filter, washing with petroleum ether and drying over phosphorus pentoxide *in vacuo*, it melted at 105°; recrystallized from water, m.p. 108°; yield 18 g. (64%).

Anal. Calcd. for $C_{12}H_{13}NO_4$: C, 61.3; H, 5.5; N, 6.0. Found: C, 61.2; H, 5.2; N, 5.9.

Cleavage of α-Amino-γ-phenoxybutyric Acid.—α-Amino-γ-phenoxybutyric acid (19.5 g., 0.1 mole) was dispersed in 60 ml. of c.b. hydroiodic acid, 250 ml. of toluene was added and the mixture refluxed for six hours with stirring. The aqueous acidic layer was then removed by azeotropic distillation while stirring was continued. The mixture was cooled, toluene removed by decantation and the remaining product purified by trituration with boiling chloroform and by subsequent prolonged continuous ether extraction in a Soxhlet, until a white-yellowish granular material was obtained. Dried over phosphorus pentoxide *in vacuo* it melted at 185–190° dec., yield 25 g. (70%).

Anal. Calcd. for $C_4H_9NO_2I_2$: C, 13.4; H, 2.5; N, 3.9; I, 71.1. Found: C, 13.5; H, 2.5; N, 4.0; I, 71.0.

By shortening the reflux time to one hour or by using only 25–28 ml. of c.b. hydroiodic acid (0.2 mole) per 19.5 g. (0.1 mole) of α-amino-γ-phenoxybutyric acid, α-amino-γ-butyrolactone hydroiodide (IV) resulted.

Cleavage of α-amino-γ-phenoxybutyric acid[6] even with a large excess of c.b. hydrobromic acid, and prolonged refluxing only produced α-amino-γ-butyrolactone hydrobromide. Moreover by heating (100°) α-amino-γ-butyrolactone hydrobromide with an excess of 65% hydrobromic acid in a sealed tube for several hours,[5a] only traces of the desired α-amino-γ-bromobutyric acid hydrobromide (VII) were obtained and most of the α-amino-γ-butyrolactone hydrobromide was recovered besides some resinous material.

α-Benzamido-γ-iodobutyric Acid (VI).—α-Benzamido-γ-butyrolactone (V) (4.1 g., 0.02 mole) was dispersed in 30 ml. of c.b. hydroiodic acid and hydrogen iodide (evolved from iodine, red phosphorus and water) was passed through at 35–40° during 15–20 minutes after complete dissolution of all of the benzamidolactone V. The solution was concentrated to dryness *in vacuo* and the residue washed with very dilute sulfurous acid, then with small portions of cold water and finally with dry ether; yield 6 g. (90%), m.p. 143–145°. The compound gave a negative ninhydrin test and no free amino nitrogen could be detected by Van Slyke analysis. Hydrolysis with 10% hydrochloric acid liberated one equivalent of benzoic acid.

Anal. Calcd. for $C_{11}H_{12}NO_3I$: C, 39.6; H, 3.6; N, 4.2; I, 38.1. Found: C, 39.8; H, 3.7; N, 4.2; I, 37.8.

Methyl α-Amino-γ-iodobutyrate Hydrochloride.—A solution of 8.92 g. (0.025 mole) of α-amino-γ-iodobutyric acid hydroiodide (II) in 200 ml. of dry methanol was saturated with dry hydrogen chloride for 2 hours at such a rate as to maintain the temperature at 35–40°. The solution was concentrated *in vacuo* until it became semi-crystalline, 200 ml. of methanol was added and it was saturated again with hydrogen chloride, as described above. The solution was then concentrated *in vacuo* to two-thirds of its volume, freed from some resinous material and again concentrated to dryness. The crude ester hydrochloride was twice dissolved in ethanol and precipitated with excess of ether; yield 4.5 g. (64%), m.p. 125°.

Anal. Calcd. for $C_5H_{11}NO_2ClI$: C, 21.4; H, 3.9; N, 5.0; Cl + I, 58.0; CH_3O, 11.1. Found: C, 21.1; H, 4.0; N, 5.2; Cl + I, 57.0; CH_3O, 11.1.

α-Amino-γ-bromobutyric Acid Hydrobromide (VII).—α-Benzamido-γ-butyrolactone (V) (6.15 g., 0.03 mole) was suspended in 50 ml. of c.b. hydrobromic acid. The mixture was cooled in an ice-bath and saturated with hydrogen bromide (final concentration of 60–65% HBr). The solution was heated in a sealed tube at 95–100° for seven hours, 50 ml. of water was added, the mixture cooled and the precipitated benzoic acid removed by filtration and subsequent extraction with ether. The filtrate was concentrated *in vacuo*, cooled and portions of pure α-amino-γ-bromobutyric acid hydrobromide (VII) were collected. The last portion, obtained from evaporation to dryness *in vacuo*, was purified from admixed α-amino-γ-butyrolactone hydrobromide by solution in cold absolute ethanol, filtration from aminolactone hydrobromide and precipitation with excess of ether; yield 5.2 g. (65%), m.p. 162–165°. α-Amino-γ-bromobutyric acid hydrobromide can be converted to α-amino-γ-butyrolactone hydrobromide by heating in water, as well as by prolonged standing in aqueous or dilute acidic solution, or in water containing alcoholic solution or by heating near the boiling point. Benzoylation and carbobenzoxylation in water–pyridine solution or in the presence of magnesium oxide led to the corresponding derivatives of the aminolactone of the γ-hydrolyzed acid.

Anal. Calcd. for $C_4H_9NO_2Br_2$: C, 18.3; H, 3.4; N, 5.3; Br, 60.8. Found: C, 18.0; H, 3.6; N, 5.2; Br, 60.5.

Methyl α-Amino-γ-bromobutyrate Hydrochloride.—α-Amino-γ-bromobutyric acid hydrobromide (VII) (6.6 g., 0.025 mole) was dissolved in 100 ml. of dry methanol. The solution was treated with hydrogen chloride and further as described for the preparation of α-amino-γ-iodobutyric acid methyl ester hydrochloride; yield 4.7 g. (81%), m.p. 128°; m.p., after purification by precipitation from absolute ethanol with ether and washing with (1:2) abs. ethanol–ether, 129–132°.

Anal. Calcd. for $C_5H_{11}NO_2ClBr$: C, 25.8; H, 4.7; N, 6.0; Cl + Br, 49.8; CH_3O, 13.3. Found: C, 26.0; H, 4.6; N, 6.0; Cl + Br, 48.9; CH_3O, 13.1.

α-Amino-γ-chlorobutyric Acid Hydrochloride (VIII).—α-Benzamido-γ-butyrolactone (V) (6.15 g., 0.03 mole) was dispersed in 50 ml. of concentrated hydrochloric acid. The mixture was cooled, saturated with hydrogen chloride (final concentration of 40% HCl) and then heated in a sealed tube at 95–100° for seven hours. Further treating conforms to the preparation of α-amino-γ-bromobutyric acid hydrobromide (VII); yield 3.6 g. (69%), m.p. 152–155°.

Anal. Calcd. for $C_4H_9NO_2Cl_2$: C, 27.6; H, 5.2; N, 8.0; Cl, 40.8. Found: C, 28.0; H, 5.3; N, 7.6; Cl, 40.1.

Methyl α-Amino-γ-chlorobutyrate Hydrochloride.—α-Amino-γ-chlorobutyric acid hydrochloride (VIII) (5.1 g., 0.03 mole) was dissolved in 100 ml. of dry methanol; the solution was treated with hydrogen chloride and then as described for the preparation of α-amino-γ-iodobutyric acid methyl ester hydrochloride; yield 3.7 g. (66%), m.p. 115–120°.

Anal. Calcd. for $C_5H_{11}NO_2Cl_2$: C, 31.9; H, 5.8; N, 7.4; Cl, 37.8; CH_3O, 16.5. Found: C, 32.0; H, 6.0; N, 7.3; Cl, 37.0; CH_3O, 16.1.

JERUSALEM, ISRAEL

(6) M. D. Armstrong, THIS JOURNAL, **70**, 1756 (1948); R. Turner, *ibid.*, **71**, 3476 (1949).