*Synthesis and Pyrolysis of N-Substituted γ-Aminobutyrates and N-Substituted Bis(β-ethoxycarbonylethyl)amines**

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Some *N*-substituted γ-aminobutyrates and *N*-substituted bis(β-ethoxycarbonylethyl)amines were synthesized and their behaviors upon pyrolysis were investigated. Ethyl *N*-benzoyl-γ-(β-ethoxycarbonylamino)butyrate (III) and ethyl γ-[bis(β-ethoxycarbonylethyl)amino]-butyrate (II) were obtained from the reaction mixture of ethyl γ-aminobutyrate and ethyl acrylate by benzoylation. Direct distillation of the mixture did not give ethyl γ-(β-ethoxycarbonylethylamino)butyrate (I), but gave *N*-(β-ethoxycarbonylethyl)-2-pyrrolidone (V). III was also derived from II by heating with benzoyl chloride as McElvain[1] did about tris-(β-ethoxycarbonylethyl)amine (XIII). V was also obtained by heating II. Both III and V gave γ-(β-carboxyethylamino)butyric acid (IV) on hydrolysis. On heating IV above its melting point, *N*-(β-carboxyethyl)-2-pyrrolidone (VI) was formed, which returned to IV by hydrolysis. IV gave ethyl *N*-ethoxycarbonyl-γ-(β-ethoxycarbonylethylamino)butyrate (VII). Reaction of ethyl β-benzylaminopropionate[2] and ethyl γ-bromobutyrate afforded ethyl *N*-benzyl-γ-(β-ethoxycarbonylethylamino)butyrate (VIII) along with a small amount of *N*-benzyl-2-pyrrolidone (IX)[3]. IX also formed on heating VIII. IX was hydrolyzed to γ-benzylaminobutyric acid (X), which reformed IX by heating. Ethyl *N*,*N*-dibenzyl-γ-aminobutyrate (XI), which was synthesized from ethyl γ-aminobutyrate and benzyl chloride, cleaved into IX and benzyl ethyl ether on heating at about 280°C. When XI was heated in acetic anhydride, it was recovered unchanged. Hydrochloride XII of XI, on the other hand, decomposed readily at about 170°C to yield IX, benzyl chloride and ethanol. Tris(β-ethoxycarbonylethyl)amine (XIII) began to decompose at about 200°C and gave ethyl acrylate, ethanol and a substance which probably could be a condensation product of β-alanine. *N*-Benzyl-bis(β-ethoxycarbonylethyl)amine (XIV)[2,4] also split ethyl acrylate at about 197°C, but the composition of the residual substance was so complicated and could not be determined. *N*-Benzoyl-bis(β-ethoxycarbonylethyl)amine (XV)[1] resisted to decompose, and gave ethyl acrylate and ethyl *N*-benzoyl-γ-aminopropionate at a higher temperature, about 304°C. (Figs. 1 and 2).

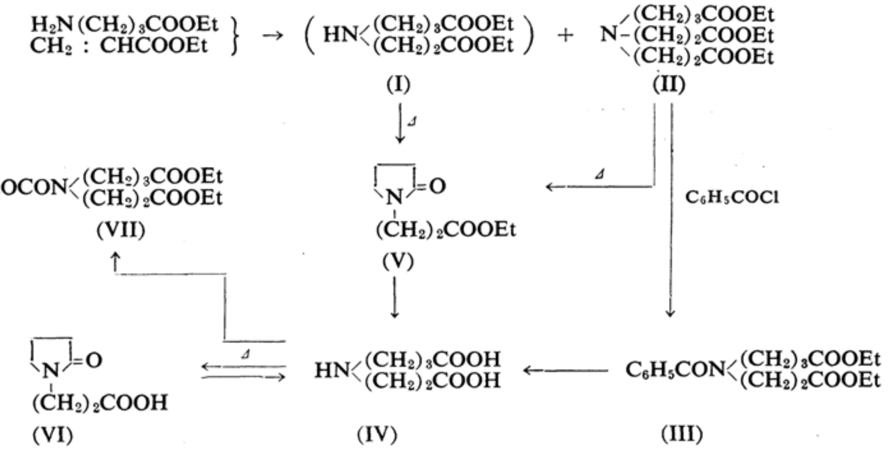

Fig. 1

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* Arranged from "Syntheses of Some Amino Acids and Amino Aldehydes", II and III (*J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zassi*), **77**, 599 (1956); ibid., **79**, 1269 (1958)).

[1] S. M. McElvain and G. Stork, *J. Am. Chem. Soc.*, **68**, 1049 (1946).

[2] G. Stork and S. M. McElvain, ibid., **69**, 971 (1947).

[3] E. Späth and J. Lintner, *Ber.*, **69**, 2730 (1936); M. W. Gittos and W. Wilson, *J. Chem. Soc.*, **1955**, 2375.

[4] J. R. Thayer and S. M. McElvain, *J. Am. Chem. Soc.*, **49**, 2862 (1927).

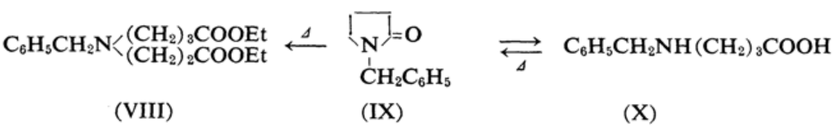

Fig. 2

Consideration of the Pyrolytic Mechanism.—The ring formation of II during the heating may be driven by the intramolecular nucleophillic attack of nitrogen to carbonyl carbon to split ethyl acrylate and form the stable five-membered ring. (Fig. 3). Likewise, in the case of VIII, XI and XII, the same mechanism was considered. Especially the pyrolysis of XII took place more readily, and this was certainly assumed to be resulted from the positively charged nitrogen, which splits benzyl cation. (Fig. 4).

The decomposition of XIII, XIV and XV was, on the other hand, considered to proceed through an ammonium compound, reversely to the additive reaction between an amino compound and ethyl acrylate. The resistance observed in the pyrolysis of XV may be due to the decrease in electron density at the nitrogen by the neighboring carbonyl group.

The liberation of ethyl acrylate in the reaction between II and benzoyl chloride, on the contrary, will proceed like Hofmann's degradative reaction as shown in Fig. 5.

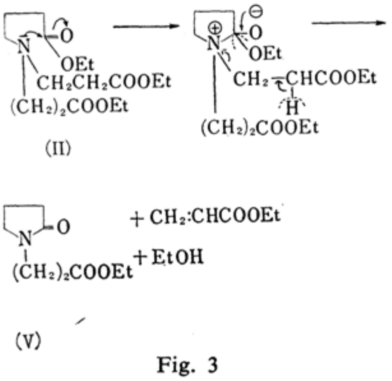

Fig. 3

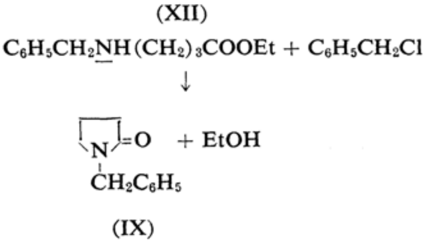

Fig. 4

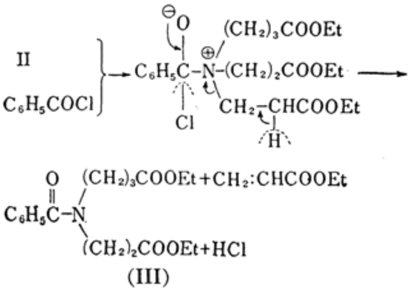

Fig. 5

Experimental

Ethyl γ-[Bis(β-ethoxycarbonylethyl)amino]butyrate (II) and Ethyl *N*-Benzoyl-γ-(β-ethoxycarbonylethylamino)butyrate (III).—To an ice-cold solution of 26.4 g. of sodium in 1 l. of absolute ethanol was added 190 g. of ethyl γ-aminobutyrate hydrochloride under stirring, followed, after 1 hr., by the addition of a solution of 115.6 g. of ethyl acrylate in 300 cc. of the same solvent. After stirring for 7 hr., the mixture was heated at 70∼73°C with stirring. The solvent was removed under reduced pressure, and 100 cc. of dry benzene was added and distilled to expel completely any of the ethanol present. A solution of 160 g. of benzoyl chloride in 250 cc. of dry benzene was added to the residue and refluxed for 20 hr. Then 100 cc. of absolute ethanol was added and refluxed for 1.5 hr. After cooling, ice was added, and the benzene layer was washed successively with cold 10% sodium hydroxide solution, water, 10% hydrochloric acid, water and 5% sodium carbonate solution, and dried over calcium chloride. Removal of benzene and distillation of the residue gave 26 g. of III as a colorless viscous oil of b. p. 200∼205°C/0.3 mmHg.

Found: C, 63.95; H, 7.46; N, 4.16. Calcd. for $C_{18}H_{25}O_5N$: C, 64.46; H, 7.51; N, 4.18%.

The above-mentioned acidic washes were united and made alkaline with sodium hydroxide solution. An oil liberated was taken up in ether and dried over calcium chloride. After removal of ether, vacuum distillation gave 129 g. of II as a colorless oil of b. p. 178∼183°C/3.0 mmHg.

Found: N, 4.17. Calcd. for $C_{16}H_{29}O_6N$: N, 4.23%.

Reaction of II with Benzoyl Chloride.—A mixture of 66.3 g. of II and 34 g. of benzoyl chloride was heated in a round-bottomed flask attached to a fractionating column in an oil bath. At about 180°C (bath temp.), ethyl acrylate began to distil, and hydrogen chloride evolved vigorously. After 5 hr. at 185∼195°C (bath temp.), 30 cc. of absolute ethanol was added to the remainder and refluxed for 1 hr. After cooling, sodium hydroxide solution was added and extracted with ether. The ethereal solution was washed successively with 2 N hydrochloric acid, water, 5% potassium carbonate solution and water. Drying with calcium chloride and distillation gave 61 g. of III, boiling at 200~205°C/0.3 mmHg. III was not obtained from II and benzoyl chloride in xylene.

***N*-(β-Ethoxycarbonylethyl)-2-pyrrolidone** (V).—a) On heating 2 g. of II in an oil bath, ethyl acrylate and ethanol began to distil at about 190°C (bath temp.). The pyrolysis completed in about 1 hr. at 195~200°C (bath temp.), and 0.7 g. of a distillate was obtained. Distillation of the remainder gave 0.9 g. of V as a colorless oil of b. p. 130~131°C/3.0 mmHg.

Found: N, 7.52. Calcd. for $C_9H_{15}O_3N$: N, 7.56%.

b) By the same procedure in the preparation of II, 60 g. of ethyl γ-aminobutyrate hydrochloride and 35.8 g. of ethyl acrylate, using 8.2 g. of sodium, were allowed to react and directly vacuum-distilled to yield 25.6 g. of V, b. p. 129~131°C/2.5 mmHg (Found: N, 7.60%).

γ-(β-Carboxyethylamino)butyric Acid (IV).—a) After a mixture of 5 g. of III and 30 cc. of 6 N hydrochloric acid was refluxed for 4 hr., it was evaporated under reduced pressure. Water was added to the residue and again evaporated. The residue was taken up in a small amount of ethanol, and acetone was added until turbidity occurred. After standing, crystals formed were collected, washed with a little ethanol. The crystals were dissolved in hot ethanol, and ether was added until the solution became turbid to afford 1.6 g. of hydrochloride of IV as hygroscopic colorless crystals of m. p. 105~106°C.

Found: N, 6.64. Calcd. for $C_7H_{13}O_4N \cdot HCl$: N, 6.63%.

A solution of 1.2 g. of the hydrochloride in 30 cc. of water was treated with an excess of silver oxide, hydrogen sulfide and was evaporated under reduced pressure. The residue was dissolved in a small amount of water, and ethanol was added. Crystals which formed on being left to stand were recrystallized as before to give 0.9 g. of free IV as colorless needles of m. p. 151~152°C (decomp.).

Found: C, 47.85; H, 7.31; N, 8.20. Calcd. for $C_7H_{13}O_4N$: C, 47.99; H, 7.48; N, 8.00%.

b) A mixture of 5 g. of V and 50 cc. of 30% barium hydroxide solution was refluxed for 5 hr. The mixture was treated with carbon dioxide and filtered. The filtrate was adjusted at pH 4.0 with sulfuric acid, filtered and evaporated under reduced pressure. The residue was dissolved in a small amount of water, and ethanol was added. The resulting solution, on standing, gave 3.7 g. of colorless crystals, melting at 151~152°C under decomposition. These did not depress their melting point on admixture with the crystals obtained in a).

c) A mixture of 0.5 g. of VI and 5 cc. of 30% barium hydroxide solution was refluxed for 5 hr. and treated as mentioned in b) to give 0.35 g. of colorless crystals of m. p. 151~152°C (decomp.). These were found to be identical with the crystals in a) by mixed fusion.

***N*-Tosyl Derivative.**—A mixture of 0.1 g. of the hydrochloride of IV and 0.2 g. of *p*-toluenesulfonylchloride in sodium hydroxide solution was stirred for 4 hr. After removal of an excessive unreacted substance by extracting with ether, the solution was acidified by hydrochloric acid and taken up in ether. Ether was expelled, and the residue was recrystallized twice from dilute ethanol to give colorless crystals of m. p. 138~139°C.

Found: N, 4.45. Calcd. for $C_{14}H_{19}O_6NS$: N, 4.24%.

***N*-(β-Carboxyethyl)-2-pyrrolidone** (VI).—a) On heating 0.2 g. of IV in an oil bath at 160~165°C for 10 min., water was lost under melting. The cooled mass was dissolved in ethanol, and ether was added until turbidity took place. Crystals which formed were recrystallized as before to afford 0.15 g. of colorless crystals of m. p. 108~109°C.

Found: N, 9.04. Calcd. for $C_7H_{11}O_3N$: N, 8.91%. Found: equivalent to sodium hydroxide (phenolphthalein as an indicator), 158.5. Calcd. 157.17.

b) The filtrate of the hydrochloride of IV, which was mentioned in a) of preparation of IV, was evaporated, and water was added. The solution was treated with silver oxide and hydrogen sulfide, and was evaporated under reduced pressure to leave a viscous oily substance. Distillation of the oily substance gave an oil of b. p. 190~195°C/0.5 mmHg, which crystallized on standing. Recrystallization from ethanol gave 0.8 g. of colorless crystals of m. p. 108~109°C. These were identified with the crystals in a) by mixed fusion.

Ethyl *N*-Ethoxycarbonyl-γ-(β-ethoxycarbonylethylamino)butyrate (VII).—To a solution of 4 g. of sodium hydroxide in 50 cc. of water was added 11 g. of ethyl chlorocarbonate under stirring and cooling with water. After stirring for 5 hr, the solution was acidified with hydrochloric acid, and extracted twice with 50 cc. of benzene and twice with 50 cc. of ether. The extracts were combined, washed with water and dried over calcium chloride. The solvent was removed completely under reduced pressure. The residue was heated on a water bath (at 60~70°C) with 5 g. of thionyl chloride for 1.5 hr., and the whole was further heated for 1 hr. with 15 cc. of absolute ethanol. Removal of ethanol and distillation of the residue gave 4 g. of a colorless oil of b. p. 163~165°C/2.0 mmHg.

Found: N, 4.60. Calcd. for $C_{14}H_{25}O_6N$: N, 4.62%.

Ethyl *N*-Benzyl-γ-(β-ethoxycarbonylethylamino)-butyrate (VIII).—A mixture of 107 g. of ethyl β-benzylaminopropionate and 50 g. of ethyl γ-bromobutyrate was left to stand for 5 days at room temperature. Ethyl γ-benzylaminopropionate hydrobromide formed was separated by filtration and washed with ether. The filtrate and the ether washings were united, and ether was removed under reduced pressure. The residue was heated on a water bath for 3 hr. and left to stand overnight. The hydrobromide again formed was treated as above. The filtrate and ether washings were united, washed with 10% sodium carbonate solution and water, and dried over calcium chloride. Evaporation of ether and vacuum distillation gave 60 g. of an oil of b. p. 171～173°C/0.1 mmHg.

Found: N, 4.42. Calcd. for $C_{18}H_{27}O_4N$: N, 4.36%.

N-Benzyl-2-pyrrolidone (IX).—On heating 0.8 g. of VIII in an oil bath at 200°C, ethyl acrylate began to smell. After holding the temperature of the bath at 265～270°C for 2 hr., the remainder was vacuum-distilled to give 0.3 g. of an oil of b. p. 142～144°C/3.0 mmHg.

Found: N, 7.83. Calcd. for $C_{11}H_{13}ON$: N, 7.99%.

γ-Benzylaminobutyric Acid (X).—A mixture of 0.3 g. of IX and 10 cc. of 30% barium hydroxide solution was refluxed for 5 hr. to cause solution of the former. The mixture was diluted with 30 cc. of water, treated with carbon dioxide while hot, and filtered. The filtrate was evaporated to dryness and taken up in absolute ethanol. Ether was added to the ethanolic solution until turbidity took place. Crystals which formed on standing were collected and recrystallized in the same way to yield 0.2 g. of colorless crystals of m. p. 139～140°C (decomp.).

Found: C, 68.10; H, 7.72; N, 7.20. Calcd. for $C_{11}H_{15}O_2N$: C, 68.37; H, 7.82; N, 7.25%.

On fractional distillation of the foreruns in the distillation of VIII, 1.5 g. of an oil of b. p. 141～142°C/3.0 mmHg was obtained. Hydrolysis of the oil as above gave colorless crystals of m. p. 139～140°C (decomp.), which did not show any depression of the melting point on adimixture with the above crystals.

Ethyl N, N-Dibenzyl-γ-aminobutyrate (XI).—To a solution of 5 g. of sodium in 200 cc. of absolute ethanol was added 37.5 g. of ethyl γ-aminobutyrate hydrochloride. After 30 min., 56.5 g. of benzyl chloride was added and the resulting mixture was refluxed for 2 hr., followed by the further heating for 20 hr. with 61 g. of anhydrous potassium carbonate. The insoluble matters were separated and washed with absolute ethanol. The filtrate and the washings were combined, and ethanol was removed. Vacuum distillation of the residue gave 13.5 g. of a colorless viscous oil of b. p. 175～177°C/1.0 mmHg.

Found: N, 4.65. Calcd. for $C_{20}H_{25}O_2N$: N, 4.50%.

Pyrolysis of XI.—a) On heating 2.8 g. of XI in an oil bath, the decomposition began at about 280°C. The distillate, which was obtained during the heating for 3 hr., was taken up in ether, washed with water and dried over calcium chloride. Evaporation of ether and distillation of the residue gave 0.7 g. of a colorless oil of b. p. 184～187°C. The oil was found to be identical with benzyl ethyl ether by infrared spectrum.

Found: C, 79.65; H, 8.59. Calcd, for $C_9H_{12}O$: C, 79.37; H, 8.83%.

The residue of the pyrolysis gave, on vacuum distillation, 0.9 g. of an oil of b. p. 142～144°C/3.0 mmHg, corresponding to IX. Crystals of m. p. 139～140°C (decomp.) were derived from the oil by the same treatment as described in the preparation of XI, and were identified with XI by mixed fusion.

b) A solution of 3 g. of XI in 25 cc. of acetic anhydride was refluxed for 4 hr. The solvent was removed under reduced pressure, and the residue was vacuum-distilled to recover 2.7 g. of an oil of b. p. 175～177°C/1.0 mmHg. The formation of benzyl ethyl ether was not appreciated thereby.

Ethyl N, N-Dibenzyl-γ-aminobutyrate Hydrochloride (XII).—Dry hydrogen chloride was passed through a solution of 7 g. of XI in absolute ethanol. The solution was evaporated to dryness under reduced pressure. The residue was dissolved in the same solvent and again evaporated. After two repetitions of this treatment, the residue was dried over potassium hydroxide in a vacuum desiccator. On being left to stand in a refrigerator, the residue became crystalline. A small amount of benzene was added, and the crystalline substances were collected. These were dissolved in a small amount of absolute ethanol, diluted by adding twice the volume of benzene, and the solution was filtered from any undissolved matter present. Addition of ether and seeding caused crystallization. The formed crystals were collected and washed with benzene to yield 6.5 g. of colorless crystals, which began to soften at 146°C with effervescence and melted clearly at 160°C.

Found: N, 3.95. Calcd. for $C_{20}H_{25}O_2N \cdot HCl$: N, 4.02%.

Pyrolysis of XII.—On heating 5 g. of XII in an oil bath at 190～200°C for 1 hr., a fraction running over at 75～78°C was collected. This was assumed to be ethanol. Then 1.6 g. of a distillate was collected during the heating at 220°C. After washing the distillate with sodium carbonate solution and water, followed by drying over calcium chloride, distillation gave 1.1 g. of a colorless oil of b. p. 176～177°C.

Found: C, 66.60; H, 5.82. Calcd. for C_7H_7Cl: C, 66.42; H, 5.54%.

The oil was found to be benzyl chloride by the following procedure. That is, a mixture of 1 g. of the oil, 1.2 g. of anhydrous potassium carbonate and 1 g. of aniline was heated at 180°C for 3 hr. Water was added to the mixture and extracted with ether. After drying over anhydrous potassium carbonate, ether was expelled, and the residue was vacuum-distilled to give an oil of b. p. 180°C/14 mmHg, which crystallized to colorless crystals of m. p. 36°C by recrystallization from ligroin. These did not depress their melting point on admixture with the specimen prepared from benzyl chloride and aniline in the same way. Both hydrochlorides, on recrystallization from ethanol and ether, gave the same crystals which softened at 201°C in green and melted at 202～203°C, turning clear light brown.

On vacuum distillation of the residue in the above pyrolysis, 1.9 g. of IX of b. p. 140～142°C/3.0 mmHg was obtained. (Found: N, 7.80%). This was converted to N-benzyl-γ-aminobutyric acid by hydrolysis as before and identified by mixed fusion with the authentic sample.

Pyrolysis of Tris(β-ethoxycarbonylethyl)amine (XIII).—On heating 10 g. of XIII in an oil bath, decomposition began to occur at about 200°C. The bath temperature was held at 210～215°C until no distillate came out. Thereby 6.9 g. of a distillate was collected, which was fractionated into four parts: b. p. 79～85°C (0.5 g.), b. p. 85～90°C (0.4 g.), b. p. 90～96°C (0.4 g.) and b. p. 96～99°C (5.1 g.) (ethyl acrylate). The residue was impossible to be distilled at 280°C (bath temp.) and 3 mmHg, but solidified on standing. A mixture of 1 g. of the residue and 6 N hydrochloric acid was refluxed for 5 hr. and evaporated under reduced pressure. The remainder was dissolved in water, treated with silver oxide and hydrogen sulfide. The resulting solution was evaporated to a smaller volume, and ethanol was added to cause crystallization. Crystals formed were collected and recrystallized from water and ethanol as before to yield 0.65 g. of colorless crystals of m. p. 197∼198°C (decomp.). These were not depressed on admixture with the authentic β-alanine.

Pyrolysis of *N*-Benzyl-bis(β-ethoxycarbonylethyl)amine (XV).—On heating 5 g. of XV in an oil bath, decomposition began to occure at about 307°C. During the heating for 2 hr. at 310∼320°C, 1.1 g. of a distillate of b. p. 95∼98°C which was assumed to be ethyl acrylate was obtained. The remainder, on vacuum distillation, gave 1.8 g. of an oil of b. p. 157∼158°C/2.5 mmHg. This was considered to be ethyl *N*-benzoyl-β-aminopropionate from the analytical values and the experiment below.

Found: C, 69.93; H, 8.42; N, 6.91. Calcd. for $C_{12}H_{17}O_2N$: C, 69.54; H, 8.27; N, 6.77%.

A mixture of 1 g. of the oil and 15 cc. of 6 N hydrochloric acid was refluxed for 4 hr. Benzoic acid which formed overnight was separated, and the filtrate was evaporated under reduced pressure. The residue was dissolved in water, treated with silver oxide and hydrogen sulfide, and again evaporated as before. The final residue was dissolved in a small amount of water, and ethanol was added to form 0.3 g. of β-alanine, melting at 197∼198°C.

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