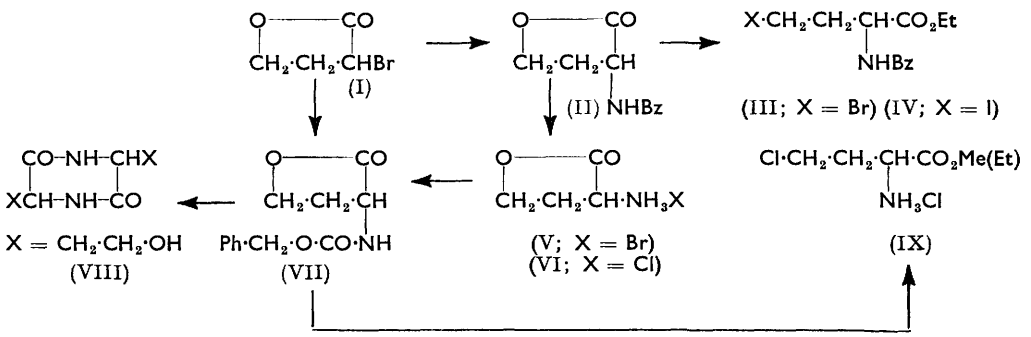
324. *Improved Preparation of Intermediates for the Syntheses of α-Aminobutyric Acid Derivatives having Functional γ-Substituents.*

By Y. KNOBLER and MAX FRANKEL.

New syntheses have been worked out for γ-halogenated derivatives of α-aminobutyric acid, intermediates for the preparation of α-amino-acids having functional γ-substituents.

THE use of trifunctional key substances bearing an exchangeable atom in the γ-positions represents the principal step in the syntheses of methionine [1,2,3] cystathionine,[4] homolanthionine,[4] canaline,[5,6] and selenium analogues of methionine and homocystine.[7] In principle, two general steps can be distinguished in synthesising such derivatives of α-aminobutyric acids by this method: the first consists in building up the trifunctional intermediate containing both the amino- and the carboxyl group either protected or inactivated by inner bonding; the second involves the introduction of the characteristic group at the γ-position. A final step is liberation from the protecting groups or cleavage of intramolecular bonds.

In our investigations it was of practical interest to render some γ-halogenated derivatives of homoserine (α-amino-γ-hydroxybutyric acid) more available; α-bromo-γ-butyrolactone (I), described by Livak *et al.*,[3] seemed to be the most suitable starting material.



From this, α-benzamido-γ-butyrolactone (II) was prepared by treatment with ammonia, alkaline hydrolysis of the resulting α-amino-γ-hydroxybutyramide, benzoylation of the sodium salt of homoserine, acidification, and heating with dilute hydrochloric acid (overall yield 60%). All these steps were carried out without isolation of intermediates.

Prolonged treatment of α-benzamido-γ-butyrolactone (II) in absolute ethanol with dry hydrogen bromide or iodide, at moderate temperatures, gave ethyl α-benzamido-γ-bromo- (or iodo)butyrate (III, 80%; IV, 75% yield). Both were used in the synthesis of DL-canaline.[6]

α-Benzamido-γ-butyrolactone (II) was debenzoylated by hydrochloric or hydrobromic acid, whereby the salts (V, VI) of α-amino-γ-butyrolactone were obtained almost quantitatively. The hydrobromide (V) represented the last intermediate in the synthesis of homoserine by E. Fischer and Blumenthal [8] and from it the dioxopiperazine (VIII) has been obtained.[3]

A different approach, also based on α-bromo-γ-butyrolactone (I), involved protection

[1] Hill and Robson, *Biochem. J.*, 1936, **30**, 248.
[2] Snyder, Andreen, Cannon, and Peters, *J. Amer. Chem. Soc.*, 1942, **64**, 2082.
[3] Livak, Britton, VanderWeele, and Murray, *ibid.*, 1945, **67**, 2218.
[4] Stekol, *J. Biol. Chem.*, 1948, **173**, 153.
[5] Kitagawa, *J. Agric. Chem. Soc. Japan*, 1936, **12**, 871.
[6] Knobler and Frankel, following paper.
[7] Painter, *J. Amer. Chem. Soc.*, 1947, **69**, 232.
[8] Fischer and Blumenthal, *Ber.*, 1907, **40**, 106.

of the amino-group of the homoserine by the benzyloxycarbonyl group. By a series of steps analogous to the preparation of α-benzamido-γ-butyrolactone (II), α-benzyloxycarbonylamino-γ-butyrolactone (VII) was obtained in 30% overall yield. α-Amino-γ-butyrolactone hydrobromide (V) gave α-benzyloxycarbonylamino-γ-butyrolactone (VII) in 63% yield (36% based on I). Removal of the protecting group by hydrogenolysis gave the free aminobutyrolactone which was dimerised to the dioxopiperazine [8] (VIII). This compound may be converted into 2 : 5-di-(2-chloroethyl)-3 : 6-dioxopiperazine, a dimeric intermediate for the preparation of α-aminobutyric acids having functional γ-substituents.[2,4] Treating the lactone (VII) with dry hydrochloric acid in absolute methanol or ethanol afforded the ester hydrochlorides (IX) of α-amino-γ-chlorobutyric acid.

Experimental

M. p.s were determined in a Fisher–Johns apparatus.

α-Benzamido-γ-butyrolactone (II).—α-Bromo-γ-butyrolactone (I) (82·5 g.) was dissolved with gentle shaking in 25% aqueous ammonia (350 ml.) at 0° and the solution was kept closed at room temperature for 6 days. N-Sodium hydroxide (1500 ml.) was added and the excess of ammonia was removed by stirring the solution in a boiling-water bath. After 2 hr. the mixture was cooled to 0°, stirred rapidly, and benzoyl chloride (210 g.) and 4N-sodium hydroxide (1 l.) were slowly added simultaneously, at such a rate that the solution remained alkaline (*ca.* 3 hr.). Stirring was then continued for 1 hr. at 0° and for 2 more hours at room temperature. Undissolved matter was removed and the filtrate diluted with water (500 ml.). 18% Hydrochloric acid (700 ml.) was added with stirring and cooling and the white foaming mixture was heated with stirring on a water-bath at 80—90° for 45 min. Heating was then discontinued but stirring continued. On reaching room temperature the reaction vessel was placed in an ice-bath and stirring continued until the crystalline mixture of α-benzamido-γ-butyrolactone and benzoic acid was precipitated. The precipitate was filtered off and dried and the lactone (II), m. p. 138°, freed from benzoic acid by washing with ether. Further crops were obtained by concentration of the mother-liquor on a steam-bath, the crystalline compound separating on cooling (m. p. 139—140°). Recrystallised from water, it had m. p. 141—142° (62 g., 60%) (Found: C, 64·1; H, 5·6; N, 6·8. Calc. for $C_{11}H_{11}O_3N$: C, 64·4; H, 5·4; N, 6·8%).

Ethyl α-Benzamido-γ-bromobutyrate (III).—α-Benzamido-γ-butyrolactone (II) (10·2 g.) was suspended in absolute ethanol [dried over $Mg(OEt)_2$] (300 ml.) and treated with dried hydrogen bromide at 40—45° for about 3 hr., during which the solid dissolved. The solution was then kept at room temperature with exclusion of moisture for 24 hr. and concentrated *in vacuo*. Some resin was filtered off from the cooled solution and the filtrate again concentrated until syrupy. It was then twice diluted by small portions of ethanol, concentrated *in vacuo*, and finally dissolved in ethanol (150 ml.). The solution was cooled to 0° and small portions of water were added with shaking and cooling until it became cloudy. The mixture was left at 0°, the *ester* separating in white fine crystals (if coloured they were purified by washing with very dilute sulphurous acid). The crystals were collected and further amounts obtained from the mother-liquor by precipitation with water as before (m. p. 75—80°). Recrystallisation from ethanol raised the m. p. to 83—84° (yield 12·6 g., 80%) (Found: C, 49·4; H, 5·1; N, 4·6; Br, 25·4; OEt, 14·4. $C_{13}H_{16}O_3NBr$ requires C, 49·7; H, 5·1; N, 4·5; Br, 25·5; OEt, 14·3%).

Ethyl α-Benzamido-γ-iodobutyrate (IV).—α-Benzamido-γ-butyrolactone (II) (10·2 g.) was treated with hydrogen iodide dried by glass wool sprayed with phosphoric oxide. A controlled rate of passage of gas and a precaution against sucking back were achieved by working under carbon dioxide atmosphere. Precipitated from ethanol with water and washed with cold 0·5% sulphurous acid, the *γ-iodobutyrate* (IV) (13·5 g., 75%) melted at 88—92°. Recrystallised from ethanol it melted at 94—95° (Found: C, 43·6; H, 4·3; N, 3·9; I, 35·0; OEt, 13·0. $C_{13}H_{16}O_3NI$ requires C, 43·2; H, 4·4; N, 3·9; I, 35·2; OEt, 12·5%).

α-Amino-γ-butyrolactone Hydrobromide (V).—α-Benzamido-γ-butyrolactone (10·25 g.) was refluxed in 15% hydrobromic acid (120 ml.) for 2 hr. From the cooled mixture, benzoic acid was removed by filtration and subsequent extraction with ether. The solution was evaporated *in vacuo* to dryness and the residue washed with small portions of absolute ethanol and ether. The hydrobromide (V) (8·5 g., 93%) had m. p. 225° (decomp.) (Found: C, 26·2; H, 4·6; N, 7·7; Br, 44·3. Calc. for $C_4H_8O_2NBr$: C, 26·4; H, 4·4; N, 7·7; Br, 43·9%).

α-Amino-γ-butyrolactone Hydrochloride (VI).—Hydrolysis of the lactone (5·1 g.) in 15% hydrochloric acid (100 ml.) gave the hydrochloride (3·3 g., 96%), m. p. 203° (decomp.) (Found: N, 9·9; Cl, 26·0. Calc. for $C_4H_8O_2NCl$: N, 10·2; Cl, 25·8%).

α-Benzyloxycarbonylamino-γ-butyrolactone (VII).—(a) *From α-bromo-γ-butyrolactone* (I). α-Bromo-γ-butyrolactone (20·6 g.) was kept in 25% aqueous ammonia (100 ml.) for 4—5 days. N-Sodium hydroxide (375 ml.) was added and the mixture heated with stirring on a boiling-water bath for 2 hr. Water (100 ml.) was added and the solution cooled to 0°. 4N-Sodium hydroxide (35 ml.) and benzyl chloroformate (25 g.) were added simultaneously in portions during 2 hr. Stirring was continued for ½ hr. with cooling and for 2 more hours at room temperature. The mixture was extracted with ether and acidified with 18% hydrochloric acid. A crude viscous layer separated which was recrystallised from hot water. The *lactone* (VII) (9 g., 30%) had m. p. 105—108° (Found: C, 61·4; H, 5·6; N, 5·8. $C_{12}H_{13}O_4N$ requires C, 61·3; H, 5·5; N, 6·0%).

(b) *From the α-amino-γ-butyrolactone hydrobromide* (V). The hydrobromide (36·4 g.) was dissolved in water (750 ml.) and cooled to 0° and pyridine (80 ml.) added with stirring. Benzyl chloroformate (39 g.) was introduced in 2 hr. and stirring was continued for 1 hr. more with cooling and 2 hr. without cooling. The product separated. It was washed with light petroleum and dried (P_2O_5) (m. p. 108—110°). Recrystallisation from ether–light petroleum raised the m. p. to 110—112° (yield 29·6 g., 63%) (Found: C, 61·3; H, 5·5; N, 5·9%).

2 : 5-*Di*-(2-*hydroxyethyl*)-3 : 6-*dioxopiperazine* (VIII).—α-Benzyloxycarbonylamino-γ-butyrolactone (VII) (4·7 g.) was suspended in absolute alcohol (100 ml.), palladium chloride on carbon (1 g.; 1 : 3) was added, and the mixture hydrogenated at 30—35°/2 atm. for 7—8 hr. The catalyst was removed, the solution concentrated until cloudy, and α-amino-γ-butyrolactone hydrochloride filtered off. Absolute ethanol (150 ml.) was added and the solution refluxed for 24 hr. It was then decolorised with Norite, filtered, concentrated *in vacuo*, and cooled, and the product collected (m. p. 186°; 0·45 g., 22%). The mother-liquor was evaporated *in vacuo*, and the viscous residue dissolved in a small amount of hot ethanol, reprecipitated by ether, and washed with small portions of cold ethanol–ether (1 : 1). This material (0·45 g., 22%) had m. p. 184° (Found: N, 13·9. Calc. for $C_8H_{14}O_4N_2$: N, 13·9%).

Methyl α-Amino-γ-chlorobutyrate Hydrochloride (IX).—α-Benzyloxycarbonylamino-γ-butyrolactone (4·7 g.) was suspended in dry methanol (150 ml.) at 50—55° and a stream of dry hydrogen chloride was passed in for 4—5 hr. during which a clear solution resulted. The methanol was removed *in vacuo*, dry ethanol was added, and the solution cooled and freed from α-amino-γ-butyrolactone hydrochloride by filtration. By addition of dry ether a mixture of the hydrochlorides of the lactone (VI) and of the ester (IX) was precipitated. Portions of cold absolute ethanol were added, the undissolved amino-lactone hydrochloride filtered off, and *methyl α-amino-γ-chlorobutyrate hydrochloride* (IX) (1·2 g., 32%), m. p. 120°, reprecipitated (Found: N, 7·2; Cl, 38·0; OMe, 16·5. $C_5H_{11}O_2NCl_2$ requires N, 7·4; Cl, 37·8; OMe, 16·5%).

By a similar procedure, on passing hydrogen chloride through an ethanolic solution of α-benzyloxycarbonylamino-γ-butyrolactone (VII), the corresponding partly crystalline *ethyl ester hydrochloride* was obtained but in poorer yield (Found: N, 6·8; Cl, 35·4; OEt, 22·5. $C_6H_{13}O_2NCl_2$ requires N, 6·9; Cl, 35·1; OEt, 22·3%). After hydrogen chloride had passed through a suspension of the lactone (VII) in ethanol without heating, the lactone was recovered. When the same reaction was carried out under reflux only α-amino-γ-butyrolactone hydrochloride was obtained.

DEPARTMENT OF ORGANIC CHEMISTRY, THE HEBREW UNIVERSITY,
JERUSALEM, ISRAEL. [*Received, December 9th*, 1957.]