and 2-chloro-5-nitrobenzotrifluoride (42 g., 0.186 mole) was added dropwise with stirring. Stirring was continued for an hour at room temperature and the alkaline mixture acidified with 6*N* hydrochloric acid to give a yellow solid. The solid was dissolved in 150 cc. of ether, the ether solution extracted with 100 cc. of 5% aqueous sodium hydroxide, then with 100 cc. of water, and both aqueous extracts were discarded. On evaporation of the ether, a yellow material precipitated. The solid crystallized from hot methanol to yield 33 g. (90%) of a substance believed to be 2,2'-bistrifluoromethyl-4,4'-dinitrodiphenyl ether, m.p. 141–141.5°. The expected product, the benzyl ether of 2-hydroxy-5-nitrobenzotrifluoride, was not detected.

Anal. Calcd. for $C_{14}H_6N_2O_5F_6$: C, 42.44; H, 1.53; N, 7.07; mol. wt., 396. Found: C, 42.01; H, 1.64; N, 7.75; mol. wt. (Rast), 410.

2-Amino-5-hydroxybenzotrifluoride. 2-Nitro-5-hydroxybenzotrifluoride[17] (40 g.), dissolved in 100 cc. of 95% ethanol, was reduced by hydrogen using 0.5 g. of 5% palladium on charcoal. The mixture was shaken for 3 hr. at room temperature. The solvent was removed leaving a residue which was recrystallized from 95% ethanol to yield 29.5 g. (86%) of 2-amino-5-hydroxybenzotrifluoride, m.p. 154.5–155.5°.

Anal. Calcd. for $C_7H_6NOF_3$: C, 47.46; H, 3.42. Found: C, 47.41; H, 3.64.

Meerwein condensation pathway for amino acids. Sodium acetate (8.5 g.), 3.0 g. of cupric chloride, 7.2 g. of acrylic acid, and 75 cc. of acetone were placed in a 500-cc. round bottomed flask containing a magnetic stirring bar. The flask was partially immersed in a Dry Ice–acetone bath and the mixture was stirred. Twenty cubic centimeters of concd. hydrochloric acid and 10 cc. of water were added to 17.7 g. (0.1 mole) of 2-amino-5-hydroxybenzotrifluoride in a beaker which was also partially immersed in a Dry Ice-acetone bath. A cold solution of 7.0 g. of sodium nitrite in 20 cc. of water was added dropwise while the mixture was stirred, the temperature being kept below 0° during the addition. The diazotized mixture was quickly added to the contents of the flask and the system connected to a mercury-bubble counter. The mixture turned green during the addition. The Dry Ice–acetone bath was removed, the system allowed to warm to room temperature and the mixture stirred for 4 hr. during which time nitrogen was evolved. Generally, bubbling ceased within 2 hr. after the bath had been removed. The contents of the flask were shaken with 150 cc. each of ether and water, the aqueous layer discarded, and 150 cc. of 10% aqueous sodium hydroxide added to the ether solution. The ether extract was discarded, the alkaline solution acidified with 6*N* hydrochloric acid and 200 cc. of ether added to the aqueous mixture. The aqueous layer was separated and the ether was evaporated by air blowing. This was continued until the odor of acrylic acid was no longer evident. The residue was dissolved in 300 cc. of concd. aqueous ammonium hydroxide and the solution placed in a 500-cc. round bottomed flask, which was stoppered. The flask and contents were shaken occasionally over a 4-day period. The contents of the flask were poured into an Erlenmeyer flask and heated on a steam bath while air was blown over the solution until the odor of ammonia could no longer be detected. The mixture was concentrated to 50 cc., powdered charcoal added and the mixture filtered. A double volume of 95% ethanol was added and the solution placed in a refrigerator. 2-Trifluoromethyltyrosine precipitated within 24 hr. After washing with cold absolute ethanol and drying, there was obtained 4.25 g. (17%) of this amino acid, m.p. 212–225° dec.; positive ninhydrin and Millon tests.

Anal. Calcd. for $C_{10}H_{10}NO_3F_3$: C, 48.20; H, 4.05; N, 5.62. Found: C, 48.36; H, 4.54; N, 5.51.

Ultraviolet Spectra. The ultraviolet spectra were obtained on a Beckman DK-2 spectrophotometer.

(17) Supplied by Maumee Chemical Co., Toledo, Ohio.

CHICAGO 16, ILL.

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

Synthesis of Peptides and of Some Polydipeptides of Homoserine by an Aminolactone Method[1]

T. SHERADSKY,[2] Y. KNOBLER, AND MAX FRANKEL

Received November 14, 1960

The use of α-amino-γ-butyrolactone and its derivatives for the synthesis of homoseryl and of *N*-homoserine peptides was investigated. Mixed homoseryl and *N*-homoserine peptides, peptidolactones and unsymmetrically substituted diketopiperazines of homoserine, as well as polymers of mixed *N*-homoserine dipeptides were synthesized.

Homoserine (α-amino-γ-hydroxybutyric acid), a precursor of methionine and of threonine,[3] was found as a bacterial degradation product of canavanine.[4] Virtanen and co-workers isolated homoserine from germinating pea seeds[5] and showed that in certain plants it occurs in peptide bound form.[6]

Various methods were developed for the synthesis of homoserine, of its derivatives as well as for conversion routes to other amino acids,[7–11] but no method was reported for the synthesis of homoserine

(1) Presented in part before the XXVIth Scientific Meeting of the Israel Chemical Society, Jerusalem, April 1960, *cf.* M. Frankel, Y. Knobler, and T. Sheradsky, *Bull. Research Council Israel*, **9A**, 59 (1960).

(2) Part of a Ph.D. Thesis to be submitted to the Hebrew University.

(3) H. J. Teas, N. H. Horowitz, and M. Fling, *J. Biol. Chem.*, **172**, 651 (1948); M. Fling and N. H. Horowitz, *J. Biol. Chem.*, **190**, 277 (1951).

(4) H. Kihara, J. M. Prescott, and E. E. Snell, *J. Biol. Chem.*, **217**, 497 (1955).

(5) A. I. Virtanen, A. M. Berg, and S. Kari, *Acta Chem. Scand.*, **7**, 1423 (1953).

(6) A. I. Virtanen and J. K. Miettinen, *Biochem. et Biophys. Acta*, **12**, 181 (1953); A. I. Virtanen, *Acta Chem. Scand.*, **11**, 747 (1957).

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

(8) J. E. Livak, E. C. Britton, J. C. Vander Weele, and M. F. Murray, *J. Am. Chem. Soc.*, **67**, 2218 (1945).

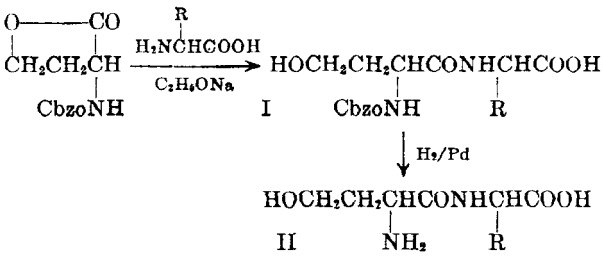
(9) Y. Knobler and M. Frankel, *J. Chem. Soc.*, 1629 (1953).

(10) M. Frankel and Y. Knobler, *J. Am. Chem. Soc.*, **80**, 3147 (1958); Y. Knobler, S. Livergand, and M. Frankel, *J. Org. Chem.*, **27**, 1794 (1959).

peptides. The preparation of the latter is complicated by the ready lactonization of this acid and of its reactive derivatives.

In this paper we describe the synthesis of homoserines peptides based on its lactones. *N*-Acylated lactones of homoserine were found active enough to react through their carbonyl, while in the free aminolactone the carboxyl and the hydroxyl groups were sufficiently protected by the lactone bond to allow production of a peptidic bond with the amino group.

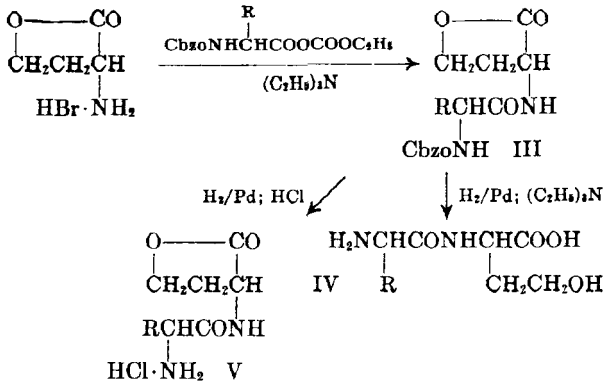
Interaction between α-benzamido-γ-butyrolactone and glycine ethyl ester led to aminolysis of the lactone with formation of the peptide bond, yielding *N*-benzoylhomoserylglycine ethyl ester. In the actual preparation, α-carbobenzoxyamino-γ-butyrolactone served as the homoserine component and sodium salts of amino acids in alcoholic solution constituted the second component. *N*-carbobenzoxyhomoseryl peptide (I) (*cf.* Table I) were obtained, which on hydrogenation yielded the free homoseryl peptides (II) (*cf.* Table II).



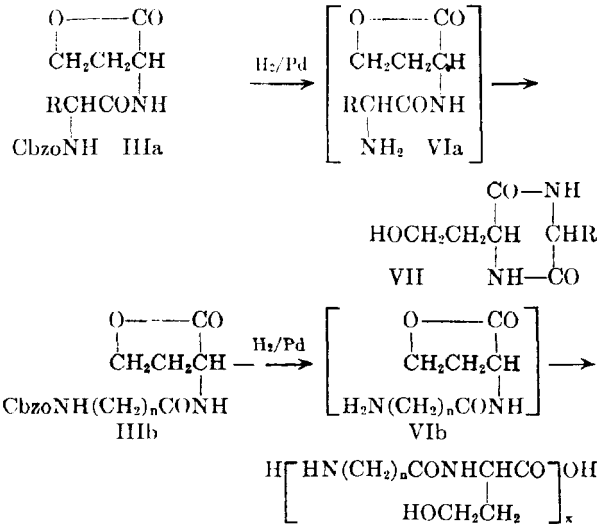
While the *N*-acylated lactones of homoserine coupled easily with amino acids, α-azido-,[11] α-phthalimido-[12] and α-dibenzylamino-γ-butyrolactone[13] were found to be inert under similar conditions. The inertness of the latter lactones can be explained by inhibition due to steric hindrance exerted by the *N*-masking groups.[13] The α-*N*-acyl group, on the other hand, increases the reactivity of the lactonic carbonyl, apparently because of the imide's tautomery in the α-acylamido group causing electron deficiency on the lactonic carbonyl, thus strengthening the nucleophilic attack on the latter.

For the synthesis of *N*-peptides of homoserine, α-amino-γ-butyrolactone was employed.

α-Amino-γ-butyrolactone hydrobromide was coupled with an *N*-carbobenzoxyamino acid by the mixed anhydride method,[14] yielding *N*-carbobenzoxypeptidolactones (III) (*cf.* Table III). On catalytic hydrogenation of III in the presence of water and triethylamine, simultaneous decarbobenzoxylation and ring opening took place, and free *N*-peptides of homoserine (IV) (*cf.* Table IV) were obtained. Hydrogenation with retention of the lactonic structure, in the presence of hydrochloric acid, gave peptidolactones hydrochlorides (V).



Removal of the carbobenzoxy rest of IIIa in a neutral medium set free the intermediate peptidolactone (VIa), which subsequently underwent intramolecular aminolysis. The lactonic ring opened under production of a cyclic mixed dipeptidic anhydride of homoserine with the second α-amino acid. Unlike the usual preparation of anhydrides from two different amino acid esters, resulting in a mixture of substituted diketopiperazines build up from one and from both starting amino acids, this method yields pure 3-(β-hydroxyethyl)-6-alkyl-2,5-diketopiperazines (VII) only (*cf.* Table V).



In peptidolactones with the free amino group located otherwise than in the α-position (IIIb), thus eliminating the possibility of forming 6-membered anhydrides, an intermolecular aminolysis took place, resulting in long chain poly(*N*-homoseryl dipeptides). Hydrogenation of α-(carbobenzoxy-β-alanylamido)-γ-butyrolactone followed by refluxing the intermediate α-(β-alanylamido)-γ-

(11) M. Frankel, Y. Knobler, and T. Sheradsky, *J. Chem. Soc.*, 3642 (1959).

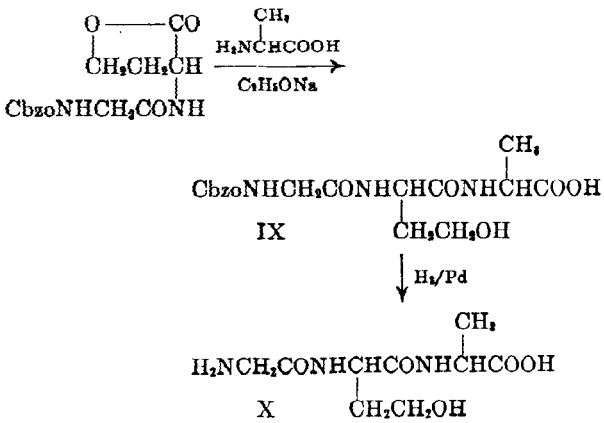
(12) M. Frankel, Y. Knobler, and T. Sheradsky, *Bull. Research Council Israel*, **7A**, 173 (1958).

(13) T. Sheradsky, Y. Knobler, and M. Frankel, *J. Org. Chem.*, in press.

(14) R. H. Boissonas, *Helv. Chim. Acta*, **34**, 874 (1951); J. R. Vaughan and R. L. Osato, *J. Am. Chem. Soc.*, **73**, 553 (1951).

butyrolactone (VIb) in ethanol yielded poly(β-alanylhomoserine) (VIIIa) of an average chain length of twenty-seven dipeptide units. Similar treatment of α-(γ-carbobenzoxyaminobutyramido)-γ-butyrolactone afforded poly(γ-aminobutyrylhomoserine) (VIIIb) of an average chain length of twenty dipeptide units. The degree of polymerization seems to decrease with elongation of the comonomeric chain, thus under identical conditions poly(ε-aminocaproylhomoserine) (VIIIc) was obtained with an average chain length of ten dipeptide units. With decreasing chain length, the polymeric products become softer, glass-like and elastic, and dissolve in cold water.

The combination of both methods presented here for the synthesis of homoseryl and of *N*-homoserine peptides, by treating the amino and the carboxyl group of α-amino-γ-butyrolactone consecutively, enables a stepwise peptide synthesis containing homoserine as linking unit. Thus, *e. g.*, interaction between α-carbobenzoxyglycylamido-γ-butyrolactone and alanine sodium salt yielded carbobenzoxyglycylhomoserylalanine (IX), and finally glycylhomoserylalanine (X).



An important advantage of the method presented here is the fact that the peptides are prepared by using intermediates of the homoserine synthesis, thus omitting the need for the preparation of the acid itself and subsequently of protected derivatives of the latter.

The further extension of the aminolactone method including synthesis of optically active compounds is under investigation.

EXPERIMENTAL

N-Benzoylhomoserylglycine ethyl ester. Glycine ethyl ester hydrochloride (7 g., 0.05 mole) was dissolved in ethanol (50 ml.), and sodium (1.15 g., 0.05 g.-atom) in ethanol (20 ml.) was added with cooling (ice salt bath). Sodium chloride was filtered off, the filtrate added to a solution of α-benzamido-γ-butyrolactone[9] (10.25 g., 0.05 mole) in ethanol (150 ml.) and left at room temperature for 1 week. It was filtered from salt and polymeric product, and concentrated *in vacuo*. After addition of ether and filtration, the product was precipitated with petroleum ether (b.p. 40–60°). It (5.5 g., 36%) was recrystallized from ethanol–petroleum ether, m.p. 114–115°.

Anal. Calcd. for $C_{15}H_{20}N_2O_5$: C, 58.4; H, 6.5; N, 9.1; OC_2H_5, 14.5. Found: C, 58.4; H. 6.7; N, 9.0; OC_2H_5, 14.7.

N-Benzoylhomoserylglycine. *N*-Benzoylhomoserylglycine ethyl ester (1.5 g.) was dissolved in 10 ml. of 1*N* sodium hydroxide solution and left to stand at room temperature for 0.5 hr., then acidified with dilute hydrochloric acid and left in the cold. After 1 week the crystals formed (0.75 g., 55%) were collected and recrystallized from ethanol–ether–petroleum ether, m.p. 153–154°.

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.6; H, 6.0; N, 9.7.

N-Carbobenzoxyhomoseryl peptides (I). The following procedure for the preparation of *N*-carbobenzoxyhomoserylalanine is typical for the coupling of α-carbobenzoxyamino-γ-butyrolactone with amino acid sodium salts. The carbobenzoxyhomoseryl peptides thus obtained are listed in Table I.

A solution of sodium (0.46 g., 0.02 g.-atom) in ethanol (50 ml.) was added to a suspension of alanine (1.8 g., 0.02 mole) in absolute ethanol (100 ml.). When most of the alanine dissolved, α-carbobenzoxyamino-γ-butyrolactone[9] (4.6 g., 0.02 mole) was added and the solution was refluxed for 4 hr. After evaporation *in vacuo* the residue was dissolved in water, unchanged lactone filtered off, and the solution acidified with 12% hydrochloric acid. The precipitate was dissolved in aqueous sodium bicarbonate, more unchanged lactone filtered off and the product of the type I (3.8 g., 58%) was precipitated by acidification in the cold. Recrystallized from water it melted at 163°.

1-Propanol could be used instead of ethanol without change in yields. With methanol or 1-butanol yields were much poorer.

Homoseryl peptides (II). The peptides freed as described below for homoserylalanine are listed in Table II.

N-Carbobenzoxyhomoserylalanine (3.2 g.) was dissolved in methanol (100 ml.). Palladium black (0.1 g.) was added and the mixture hydrogenated for 4 hr. at 3 atm. The catalyst was removed by filtration and the solvent distilled off *in vacuo*. The residue was recrystallized from water-acetone (1.9 g., 100%), m.p. 184–185° dec.

α-Amino-γ-butyrolactone hydrobromide was prepared by a method previously described,[11] modified for larger quantities. Crude α-azido-γ-butyrolactone (137 g.) was dissolved in glacial acetic acid (500 ml.) and dry hydrogen bromide was passed through for 5 hr. The precipitate was collected and washed with ether. It weighed 75 g., m.p. 223–224°.

Carbobenzoxypeptidolactones (III). The following procedure for the preparation of α-carbobenzoxyglycylamido-γ-butyrolactone is typical for the preparation of the carbobenzoxypeptidolactones listed in Table III.

A solution of carbobenzoxyglycine (10.5 g., 0.05 mole) and triethylamine (5.1 g., 0.05 mole) in toluene (100 ml.) was cooled to −5°, ethyl chloroformate (5.4 g., 0.05 mole) added, and the mixture stirred in the cold for 20 min. A solution of α-amino-γ-butyrolactone hydrobromide (9.1 g., 0.05 mole) and triethylamine (10.2 g., 0.1 mole) in chloroform (100 ml.) was added. Stirring in the cold was continued for 15 min. and the mixture left overnight at room temperature. The precipitated salt, sometimes mixed with a portion of the product, was filtered off and the water insoluble portion collected. The mother liquor was washed with water then with aqueous sodium bicarbonate, dried (magnesium sulfate), and evaporated *in vacuo*. Crystallized from water, the product (8.6 g., 66%) melted at 108°.

N-Peptides of homoserine (IV). These peptides are prepared as described below for glycylhomoserine and are listed in Table IV.

α-Carbobenzoxyglycylamido-γ-butyrolactone (1.45 g.) was dissolved in 75 ml. of 50% aqueous ethanol. Triethylamine (5 ml.) and palladium black (0.2 g.) were added and the mixture hydrogenated for 2 hr. at 3 atm. The catalyst was filtered off and the solvent evaporated *in vacuo* below

TABLE I

N-CARBOBENZOXYHOMOSERYLPEPTIDES (I)

HOCH$_2$CH$_2$CHCONHCHCOOH
(CbzoNH on the first CH; R on the second CH)

Amino Acid–	M.P.	Yield, %	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
DL-Alanine	163	58	$C_{15}H_{20}N_2O_6$	55.6	55.6	6.2	6.1	8.6	8.6
β-Alanine	125–127	42	$C_{15}H_{20}N_2O_6$	55.6	55.8	6.2	6.2	8.6	8.3
L-Leucine	Oil	49	$C_{18}H_{26}N_2O_6$	59.0	58.6	7.1	7.2	7.7	7.3
DL-Phenylalanine	144–146	62	$C_{21}H_{24}N_2O_6$	63.0	62.8	6.0	5.8	7.0	6.9
DL-Serine	128–129	44	$C_{15}H_{20}N_2O_7$	52.9	52.9	5.9	5.6	8.2	8.0

TABLE II

HOMOSERYL PEPTIDES (II)

HOCH$_2$CH$_2$CHCONHCHCOOH
(NH$_2$ on the first CH; R on the second CH)

Amino Acid–	M.P., Dec.	Formula	C Calcd.	C Found	H Calcd.	H Found	N (Kjeldahl) Calcd.	N (Kjeldahl) Found	N (Van Slyke) Calcd.	N (Van Slyke) Found
DL-Alanine	184–185	$C_7H_{14}N_2O_4$	44.2	44.3	7.4	7.4	14.7	14.5	7.4	7.2
β-Alanine	187–188	$C_7H_{14}N_2O_4$	44.2	44.4	7.4	7.6	14.7	14.4	7.4	7.5
L-Leucine	213–215	$C_{10}H_{20}N_2O_4$	51.7	51.9	8.6	8.7	12.1	12.2	6.0	6.0
DL-Phenylalanine	209–210	$C_{13}H_{18}N_2O_4$	58.6	58.8	6.8	6.9	10.5	10.2	5.3	5.3
DL-Serine	181–185	$C_7H_{14}N_2O_5$	40.8	40.2	6.8	7.0	13.6	13.6	6.8	7.1

TABLE III

CARBOBENZOXYPEPTIDOLACTONES (III)

O——CO   NHCbzo
CH$_2$CH$_2$CHNHCOCHR
(ring: O joined to the first CH$_2$, CO joined to the ring CH; NHCbzo on CHR)

Amino Acid–	M.P.	Yield, %	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
DL-Alanyl	162	73	$C_{15}H_{18}N_2O_5$	58.8	58.7	5.9	6.0	9.2	9.4
β-Alanyl	146–147	64	$C_{15}H_{18}N_2O_5$	58.8	58.9	5.9	5.8	9.2	9.4
γ-Aminobutyryl	107	52	$C_{16}H_{20}N_2O_5$	60.0	60.5	6.3	6.5	8.8	8.6
ε-Aminocaproyl	92–93	73	$C_{18}H_{24}N_2O_5$	62.1	62.1	6.9	6.5	8.0	7.8
Glycyl	108	66	$C_{14}H_{16}N_2O_5$	57.5	57.2	5.5	5.5	9.6	9.6
DL-Phenylalanyl	134–135	56	$C_{21}H_{22}N_2O_5$	66.0	66.4	5.8	6.1	7.3	7.5

TABLE IV

N-PEPTIDES OF HOMOSERINE (IV)

H$_2$NCHCONHCHCOOH
(R on the first CH; CH$_2$CH$_2$OH on the second CH)

Amino Acid–	M.P., Dec.	Yield, %	Formula	C Calcd.	C Found	H Calcd.	H Found	N (Kjeldahl) Calcd.	N (Kjeldahl) Found	N (Van Slyke) Calcd.	N (Van Slyke) Found
DL-Alanyl	201–202	38	$C_7H_{14}N_2O_4$	44.2	44.3	7.4	7.5	14.7	14.8	7.4	7.3
β-Alanyl	190–191	85	$C_7H_{14}N_2O_4$	44.2	44.0	7.4	7.4	14.7	14.4	7.4	7.1
Glycyl	194–196	30	$C_6H_{12}N_2O_4$	40.9	40.7	6.8	7.1	15.9	15.6	8.0	8.3
DL-Phenylalanyl	202	25	$C_{13}H_{18}N_2O_4$	58.6	58.4	6.8	6.9	10.5	10.2	5.3	5.1

40° to a small volume. Acetone was added, the precipitated oil was dissolved in water and precipitated again with acetone. After standing overnight in the cold it crystallized in needles (0.6 g., 30%), m.p. 194–196° dec.

Longer hydrogenation time or evaporation to dryness gave only the diketopiperazines VII. The formation of VII from the competitive free peptidolactone VIa is responsible for the low yields of the dipeptides IV.

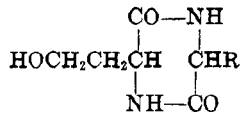
α-Glycylamido-γ-butyrolactone hydrochloride (V. R = H). α-Carbobenzoxyglycylamido-γ-butyrolactone (1.45 g.) was dissolved in ethanol (50 ml.), concd. hydrochloric acid (1 ml.) and palladium black (0.1 g.) were added and the mixture hydrogenated for 4 hr. at 3 atm. The catalyst was filtered off and the solvent removed *in vacuo*. Crystallization of the residue from ethanol-ether afforded the product (0.8 g., 40%), m.p. 179–182°.

Anal. Calcd. for $C_6H_{11}N_2O_3Cl$: C, 37.0; H, 5.7; N (Kjeldahl), 14.4; N (Van Slyke), 7.2. Found: C, 36.7; H, 5.9; N (Kjeldahl), 14.6; N (Van Slyke), 7.4.

α-Alanylamido-γ-butyrolactone hydrochloride (V. R =

TABLE V

3-(β-HYDROXYETHYL)-6-ALKYL-2,5-DIKETOPIPERAZINES (VII)



R	Amino Acid	M.P.	Formula	C		H		N	
				Calcd.	Found	Calcd.	Found	Calcd.	Found
H	Glycine	162	$C_6H_{10}N_2O_3$	45.6	45.6	6.3	6.3	17.7	17.6
CH_3	DL-Alanine	178	$C_7H_{12}N_2O_3$	48.8	48.7	7.0	7.0	16.3	16.2
$CH_2C_6H_5$	DL-Phenylalanine	215	$C_{13}H_{16}N_2O_3$	62.9	63.1	6.5	6.9	11.3	11.2

CH_3) was prepared as above, yield 55%, m.p. 225–228° (dec.).

Anal. Calcd. for $C_7H_{13}N_2O_3Cl$: N (Kjeldahl), 13.4; N (Van Slyke), 6.7. Found: N (Kjeldahl), 13.6; N (Van Slyke), 6.7.

3-(β-Hydroxyethyl)-6-alkyl-2,5-diketopiperazines (VII). The following procedure is general for the synthesis of substituted diketopiperazines build up from homoserine and a different α-amino acid, listed in Table V.

α-Carbobenzoxyglycylamido-γ-butyrolactone (2.9 g.) was dissolved in ethanol (100 ml.), palladium black (0.1 g.) added and the mixture hydrogenated for 4 hr. at 3 atm. The catalyst was removed by filtration, the filtrate refluxed for 10 hr. and evaporated *in vacuo*. The residue was crystallized from ethanol–ether–petroleum ether to give the diketopiperazine of type VII (0.7 g., 92%), m.p. 162°.

Poly(β-alanylhomoserine) (VIIIa). α-(Carbobenzoxy-β-alanylamido)γ-butyrolactone (1.55 g.) was dissolved in ethanol (50 ml.) and palladium black (0.1 g.) added. The mixture was hydrogenated for 4 hr. at 3 atm. and the catalyst filtered off. The solution was refluxed for 20 hr. during which time the polymer separated. Soluble in boiling water, in hot acetic acid, precipitable from water-acetone. It (0.6 g., 70%) decomposed at 325–330° without melting.

Anal. Calcd. for $(C_7H_{12}N_2O_3)_x$: C, 48.8; H, 7.0; N, 16.3. Found: C, 48.6; H, 6.8; N (Kjeldahl), 15.9; N (Van Slyke), 0.3.

The terminal nitrogen value indicates an average chain length of 27 dipeptide units.

Poly(γ-aminobutyrylhomoserine) (VIIIb). The polymer was prepared in the same way as VIIIa, starting with α-(γ-carbobenzoxyaminobutyrylamido)-γ-butyrolactone. It decomposes at 280–290°. Its properties are similar to VIIIa.

Anal. Calcd. for $(C_8H_{14}N_2O_3)_x$: N (Kjeldahl), 15.1; N (Van Slyke, x = 21), 0.36. Found: N (Kjeldahl), 15.2; N (Van Slyke), 0.35.

Poly(ε-aminocaproylhomoserine) (VIIIc) was prepared as described for the former polydipeptides, starting with α-(ε-carbobenzoxyaminocaproylamido)-γ-butyrolactone. The product was obtained by evaporation of the ethanolic polymerization solution, as soft, glassy, elastic fiber forming mass. It was soluble in cold water, acetic acid, and alcohol. It precipitated from acetic acid and ether, but could not be crystallized as the former polymers. The crude product has an average chain length of ten units, as indicated by the terminal nitrogen values.

Carbobenzoxyglycylhomoserylalanine (IX). α-Carbobenzoxyglycylamido-γ-butyrolactone (2.9 g., 0.01 mole) was added to a solution of sodium (0.23 g., 0.01 g. atom) and alanine (0.89 g., 0.01 mole) in 50 ml. of ethanol and the solution refluxed for 4 hr. The ethanol was removed *in vacuo* and the residue dissolved in water. Acidification with 12% hydrochloric acid precipitated an oily material, which was reprecipitated from ethyl acetate–petroleum ether giving a semisolid product (2.5 g., 65%).

Anal. Calcd. for $C_{17}H_{23}N_3O_7$: N, 11.0. Found: N, 10.9.

Glycylhomoserylalanine (X). IX (1.7 g.) was dissolved in methanol (50 ml.), palladium black (0.05 g.) added and the mixture hydrogenated for 4 hr. at 3 atm. After removal of the catalyst and evaporation of the solution *in vacuo*, the residue was crystallized from water-acetone yielding the free tripeptide (X) (1 g., 80%), m.p. 188–190° dec.

Anal. Calcd. for $C_9H_{17}N_3O_5$: N (Kjeldahl), 17.0; N (Van Slyke), 5.7. Found: N (Kjeldahl), 16.7; N (Van Slyke), 5.6.

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