heated under reflux for one hour. At the end of this time the hot reaction mixture was filtered rapidly through a hot Buchner funnel. The filtrate on cooling deposited crystals of the desired hydrochloride. Completion of the precipitation was accomplished by adding ether. The product was recrystallized from ethanol.

Preparation of the S-Substituted-2-imidazolidinethiones.—A solution of 0.1 mole of the hydrochloride in 50 ml. of water was cooled in an ice-bath and treated with 35 ml. of a 25% solution of ammonium hydroxide. The precipitate which appeared immediately was collected on a Buchner funnel and was recrystallized from ethanol or better from a mixture of benzene and methylcyclohexane.

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Optical Rotation of Peptides. I. Glycine and Alanine Dipeptides[1]

BY BERNARD F. ERLANGER AND ERWIN BRAND

The optical rotation of peptides may be considered an additive function of the contributions of the asymmetric carbon atoms of the constituent amino acid residues. It can be interpreted on the assumption that the contributions to the total rotation by an L- and by a corresponding D-amino acid residue are numerically the same, but opposite in sign.[2] As a first approach to this problem, a number of isomeric glycine and alanine dipeptides were synthesized and their optical rotation determined in the state NH_3^+, COO^- (in H_2O) and also in the state NH_3^+, COOH (in HCl). These dipeptides were first synthesized in the early years of this century by Emil Fischer[3] from α-halogen acid halides and about thirty years later by Bergmann[3] and collaborators from carbobenzoxy amino acid chlorides. We have used as starting materials the carbobenzoxy hydrazides of glycine and of alanine. These stable hydrazides are converted by the Bergmann technique[3] into their azides, which are coupled with amino acid ethyl or benzyl esters to yield carbobenzoxy dipeptide esters. The ethyl esters are either converted into carbobenzoxy dipeptide hydrazides or saponified to carbobenzoxy dipeptides, which are hydrogenated to the free dipeptides. The carbobenzoxy dipeptide benzyl esters are directly hydrogenated to dipeptides.

The specific rotation of six dipeptides, in H_2O and in 0.5 *N* HCl, is shown in Table II; the values in H_2O agree with those found by Emil Fischer[3] and Max Bergmann.[3] More detailed data on the specific rotation of these peptides and on the *residue rotations*[2] of alanine residues will be reported subsequently.

Experimental

Starting Materials. Carbobenzoxyamino Acid Hydrazides.—The preparation and properties of the glycine and alanine derivatives are reported, since these compounds have not been previously described.[4] The procedures used follow in a general way those given by Bergmann[5] for the corresponding lysine derivative. The carbobenzoxy hydrazides of glycine and of alanine are stable compounds.

1. **Carbobenzoxyglycine Hydrazide.**—Into a 500-cc. 3-neck flask equipped with a stirrer and immersed in an ice–salt-bath are placed 13.0 g. (0.1 mole) glycine ethyl ester hydrochloride, 75 cc. of water and 180 cc. of $CHCl_3$. With vigorous stirring, 5.2 g. (0.13 mole) of MgO is added in three portions over a period of 30 minutes, while 22.2 g. (0.13 mole) of carbobenzoxy chloride is dropped in. Stirring is continued for another 30 minutes, when 5 cc. of pyridine is added, followed in five minutes by acidification (congo) with 5 *N* HCl. The $CHCl_3$ layer is separated, washed first with 0.5 *N* HCl, then successively with water, 5% $NaHCO_3$, and water, dried over Na_2SO_4 and taken down *in vacuo*. The resulting oil is repeatedly (three times) treated with 50 cc. of anhydrous ethanol, which each time is distilled off *in vacuo*. The oil (carbobenzoxyglycine ethyl ester) is then dissolved in 100 cc. of anhydrous ethanol, 7 g. of hydrazine hydrate added, and the mixture allowed to stand overnight at room temperature. Most of the hydrazide crystallizes; it is filtered off, washed with cold anhydrous ethanol and dried; yield 15.2 g., m.p. 115°. Another 3.5 g. is recovered from the mother liquor; total yield 84%, based on glycine ethyl ester hydrochloride. For analysis the product is recrystallized from ethyl acetate; m.p. 115.5° (all m.p. cor.).

Anal. Calcd. for $C_{10}H_{13}O_3N_3$ (223.2): N, 18.8. Found: N, 18.9.

2. **Carbobenzoxy-L-alanine Hydrazide.**—The specific rotation $[\alpha]^{25}D$ of the alanine used in these and other syntheses varied from +14.5 to +14.7° for the L-isomer and from −14.4 to −14.7° for the D-isomer (2% in 6 *N* HCl). Most of the L- and D-alanine was prepared from acetyl-DL-alanine by Greenstein's enzymic resolution method[6] which made possible the preparation of relatively large batches.[7]

The carbobenzoxy hydrazide of L-alanine is prepared by the procedure described above for the corresponding glycine derivative and recrystallized from ethyl acetate. Total yield from 15.4 g. (0.1 mole) of L-alanine ethyl ester hydrochloride equals 18.7 g. (79%); m.p. 138.5°; $[\alpha]^{25}D$ −28.6° (2% in 0.5 *N* HCl).

Anal. Calcd. for $C_{11}H_{15}O_3N_3$ (237.3): N, 17.7. Found: N, 17.8.

3. **Carbobenzoxy-D-alanine Hydrazide.**—This compound is obtained from D-alanine ethyl ester hydrochloride by the same procedure and in the same yield as the corresponding L-derivative; m.p. 138.5°; $[\alpha]^{25}D$ +28.7° (2% in 0.5 *N* HCl).

Anal. Found: N, 17.7.

Amino Acid Benzyl Esters.—The use of amino acid benzyl esters[8] simplifies the "Carbobenzoxy" method for peptide synthesis, which involves the coupling of carbobenzoxy chlorides or azides with free amino acid esters. As is well known, the benzyl esters save one step in this synthesis, because the benzyl group is removed simultaneously with the N-carbobenzoxy groups by catalytic hydrogenation to yield free peptides, whereas other ester groups have to be saponified before hydrogenation. Moreover, the saponification of methyl and ethyl esters of carbobenzoxy peptides becomes increasingly difficult as the peptide chain is lengthened and the number of N-carbobenzoxy groups increased.[9]

The benzyl ester hydrochlorides of hydroxyproline,[10] of glycine and of cysteine (hydro-iodide[11]) have been well characterized. The γ-benzyl esters of both L- and D-glutamic acid were recently synthesized by Hanby, *et al.*,[12] by esterification of the amino acid with benzyl alcohol in the presence of constant-boiling hydriodic acid. Hydroxyproline[10] can be esterified with benzyl alcohol and dry HCl, but

(1) This report is part of a dissertation submitted by Bernard F. Erlanger in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University. Presented in part before the Division of Biological Chemistry at the 118th Meeting of the A.C.S., Chicago, Ill., September, 1950.

(2) Brand and Erlanger, THIS JOURNAL, **72**, 3314 (1950).

(3) For references *cf.* Fruton, *Adv. Prot. Chem.*, **5**, 1 (1949).

(4) Since this paper went to press, Simmons, Harris and Fruton (*J. Biol. Chem.*, **188**, 251 (1951)) have reported the synthesis of carbobenzoxyglycinhydrazide (m.p. 116–117°) by a somewhat different procedure.

(5) Bergmann, Zervas and Greenstein, *Ber.*, **65**, 1692 (1932).

(6) Fodor, Price and Greenstein, *J. Biol. Chem.*, **178**, 503 (1949).

(7) For some enzyme preparations we are indebted to Armour and Company. We gratefully acknowledge the coöperation of Dr. Greenstein, who gave us part of the alanine and helped B.F.E. prepare the rest in the National Cancer Institute laboratories.

(8) Bergmann, Zervas and Ross, *J. Biol. Chem.*, **111**, 245 (1935), footnote 1.

(9) Braxd and Erlanger, unpublished experiments.

(10) Smith and Bergmann, *J. Biol. Chem.*, **153**, 627 (1947); they did not obtain proline benzyl ester in analytically pure form.

(11) Harington and Mead, *Biochem. J.*, **30**, 1598 (1936).

(12) Hanby, Waley and Watson, *J. Chem. Soc.*, 3239 (1950).

TABLE I

GLYCINE AND ALANINE DIPEPTIDE DERIVATIVES

No.	Compound[a]	Molecular formula	Mol. wt.	M.p., °C. cor.	N, % Calcd.	N, % Found	Neut. equiv.[b] Found
		Carbobenzoxy dipeptide esters					
7	Z.Gly-Ala.OEt (L)[c]	$C_{15}H_{20}O_5N_2$	308.3	65	9.1	9.0	
8	Z.Gly-Ala.OEt (D)	$C_{15}H_{20}O_5N_2$	308.3	66	9.1	9.0	
9	Z.Ala-Gly.OEt (L)[d]	$C_{15}H_{20}O_5N_2$	308.3	100			
10	Z.Ala-Gly.OBz (L)	$C_{20}H_{22}O_5N_2$	370.4	111	7.6	7.6	
11	Z.Ala-Gly.OBz (D)	$C_{20}H_{22}O_5N_2$	370.4	112	7.6	7.6	
12	Z.Ala-Ala.OEt (L-L)[e]	$C_{16}H_{22}O_5N_2$	322.4	116			
13	Z.Ala-Ala.OBz (L-L)	$C_{21}H_{22}O_5N_2$	384.4	138	7.3	7.3	
14	Z.Ala-Ala.OEt (D-D)	$C_{16}H_{22}O_5N_2$	322.4	116	8.7	8.7	
15	Z.Ala-Ala.OEt (L-D)	$C_{16}H_{22}O_5N_2$	322.4	92	8.7	8.7	
16	Z.Ala-Ala.OEt (D-L)	$C_{16}H_{22}O_5N_2$	322.4	92	8.7	8.7	
		Carbobenzoxy dipeptide hydrazides					
17	Z.Ala-Ala.$NHNH_2$ (L-L)	$C_{14}H_{20}O_4N_4$	308.4	209	18.3	18.2	
18	Z.Ala-Ala.$NHNH_2$ (D-D)	$C_{14}H_{20}O_4N_4$	308.4	208	18.3	18.2	
19	Z.Ala-Ala.$NHNH_2$ (L-D)	$C_{14}H_{20}O_4N_4$	308.4	193	18.3	18.3	
20	Z.Ala-Ala.$NHNH_2$ (D-L)	$C_{14}H_{20}O_4N_4$	308.4	193	18.3	18.3	
		Carbobenzoxy dipeptides					
21	Z.Gly-Ala.OH (L)[f]	$C_{13}H_{16}O_5N_2$	280.2	119.5	10.0	10.0	279
22	Z.Gly-Ala.OH (D)[g]	$C_{13}H_{16}O_5N_2$	280.2	119	10.0	10.0	280
23	Z.Ala-Ala.OH (D-D)	$C_{14}H_{18}O_5N_2$	294.3	153	9.5	9.6	297
24	Z.Ala-Ala.OH (L-D)	$C_{14}H_{18}O_5N_2$	294.3	116.5	9.5	9.6	294

[a] The following abbreviations are used (*cf.* Brand, *Ann. N. Y. Acad. Sci.*, **47**, 187 (1946); Brand and Edsall, *Ann. Rev. Biochem.*, **16**, 224 (1947); *Biochem. J.*, Suggestions to Authors, p. 3 (1949): Z: carbobenzoxy, $C_6H_5{\cdot}CH_2OCO$ Gly: $NH(CH_2)CO$; Ala: $NH(CHCH_3)CO$; peptide linkage indicated by hyphen: -; Et: C_2H_5; Bz: $C_6H_5CH_2$; configuration follows compound in parentheses: ( ). *E.g.*, carbobenzoxy-D-alanyl-L-alanine ethyl ester: Z.Ala-Ala.OEt (D-L); L-Alanyl-D-alanine: H.Ala-Ala.OH (L-D). [b] Neut. equiv.: neutralization equivalent by titration in alcohol.[20] [c] Previously prepared (*cf.* Bergmann and Zervas, *J. Biol. Chem.*, **113**, 341 (1936)) from carbobenzoxyglycyl chloride with m.p. 59°. [d] Previously prepared (*cf.* Bergmann, *et al.*, *J. Biol. Chem.*, **109**, 325 (1935)) from carbobenzoxyalanyl chloride with the same m.p. [e] Previously prepared (*cf.* Stein, Moore and Bergmann, *J. Biol. Chem.*, **154**, 191 (1944)) from carbobenzoxyalanyl chloride with the same m.p. [f] $[\alpha]^{24}D$ −10.2° (2.8% in alcohol); previously prepared by Abderhalden and Neumann (*Fermentforschung*, **14**, 133 (1934)) with m.p. 155–156° and $[\alpha]^{20}D$ −6.4° (3% in alcohol) and by Bergmann and Fruton (*J. Biol. Chem.*, **117**, 189 (1937)) with m.p. 135° and $[\alpha]^{23}D$ −9.5° (5% in alcohol). [g] $[\alpha]^{23}D$ +10.1° (2.9% in alcohol), previously prepared (*cf.* Bergmann and Fruton, *J. Biol. Chem.*, **117**, 189 (1937)) with m.p. 135° and $[\alpha]^{23}D$ +9.3° (5% in alcohol).

TABLE II

GLYCINE AND ALANINE DIPEPTIDES ANALYTICAL DATA AND SPECIFIC ROTATION

No.	Compound[a]	Molecular formula	Mol. wt.	N, % Calcd.	N, % Found	Amino N, % Calcd.	Amino N, % Found	Neut. equiv.[b] Found	$[\alpha]D$, c = 2 H_2O 25° Literature	$[\alpha]D$, c = 2 H_2O 25° authors	0.5 *N* HCl 24° Authors
25	H.Gly-Ala.OH (L)	$C_5H_{10}O_3N_2$	146.2	19.2	19.2	[c]		144	−50[d]	−50.4	−59.3[k]
26	H.Ala-Gly.OH (L)	$C_5H_{10}O_3N_2$	146.2	19.2	19.2	9.6	9.6	145	+50.0[e] +50.3[f]	+50.6	+22.6
27	H.Ala-Gly.OH (D)	$C_5H_{10}O_3N_2$	146.2	19.2	19.2	9.6	9.5	144		−50.4[j]	−23.5
28	H.Ala-Ala.OH (L-L)[m]	$C_6H_{12}O_3N_2$	160.2	17.5	17.3	8.7	8.6	160	−21.7[g] −21.6[h]	−21.2	−37.3
29	H.Ala-Ala.OH (D-D)[m]	$C_6H_{12}O_3N_2$	160.2	17.5	17.4	8.7	8.7	160		+21.3	+37.9
30	H.Ala-Ala.OH (L-D)	$C_6H_{12}O_3N_2$	160.2	17.5	17.5	8.7	8.8	159	+68.94[i]	+71.2	+74.1[l]

[a,b] See Table I. [c] The value for amino nitrogen obtained in the manometric Van Slyke apparatus is too high, as is usual for peptides containing a terminal glycine amino group. [d] 8.7% at 20° (*cf.* Fischer and Schulze, *Ber.*, **40**, 943 (1907)). [e] 4% at 27° (see Table I, footnote *e*). [f] 10% at 18° (*cf.* Fischer, *Ber.*, **41**, 850 (1908)); [g] 5% at 24° (see Table I, footnote *e*). [h] 5% at 20° (*cf.* Fischer, *Ber.*, **39**, 453 (1906)). [i] 7.5% at 20° (*cf.* Fischer and Raske, *Ber.*, **39**, 3981 (1906)); [j] At 24°. [k] At 25°. [l] At 23°. [m] X-Ray studies on these crystals carried out by Dr. R. E. Pasternak in Dr. Pauling's Laboratory at the California Institute of Technology will be published by these authors.

this method gives an impure product in poor yield in the case of glycine.[13] Glycine benzyl ester hydrochloride[11,14] has been prepared in better yield from glycyl chloride hydrochloride.[15] Bergmann states[3] that amino acid carbamino anhydrides (Leuch's anhydrides) were frequently used in his laboratory for the preparation of amino acid benzyl esters, but he published no details.

For the Bergmann synthesis of amino acid benzyl esters, all reagents must be dry and moisture carefully excluded from all operations and filtrations (immersion filter) until the crystalline benzyl ester hydrochlorides are ready to be collected.

4. Glycine Benzyl Ester Hydrochloride.—To a mechanically stirred suspension of 12.6 g. (0.06 mole) of carbobenzoxy glycine[16] in 110 cc. of ether (300-cc. 3-neck flask, ice–salt-bath) is added 15 g. (0.07 mole) of PCl_5 over a pe-

(13) Abderhalden and Suzuki, *Z. physiol. Chem.*, **176**, 101 (1928).
(14) Ruggli, Ratti and Henzi, *Helv. Chim. Acta*, **12**, 361 (1929).
(15) Fischer, *Ber.*, **38**, 2914 (1905).
(16) Bergmann and Zervas, *ibid.*, **65**, 1192 (1932).

riod of 15 minutes; stirring is continued for an additional 20 minutes. From the undissolved excess PCl_5 the solution is filtered into a still and the ether removed *in vacuo* (bath temperature maintained throughout at 60°). In order to remove $POCl_3$, 75 cc. of ethyl acetate is added and then distilled off. The ethyl acetate treatment is repeated four times. The last portion of ethyl acetate is distilled off *in vacuo* until about 40 cc. of distillate has been collected. The residue is cooled in an ice-bath and treated with 25 cc. of petroleum ether. After one hour the supernatant is removed by suction and the residue (mostly dense crystals of glycine carbamino anhydride[17]) washed twice with 25 cc. of petroleum ether. The anhydride is then transferred with 30 cc. of benzyl alcohol to a 500-cc. flask containing 200 cc. of ether, previously saturated with HCl at 0°. On warming to 25° while stirring magnetically, CO_2 evolution begins and the benzyl ester hydrochloride starts to crystallize as long needles, while the anhydride dissolves. After continuing magnetic stirring overnight at 25°, the hydrochloride is filtered off without special precautions and washed with ether (9.5 g., m.p. 137–138°). Recrystallization from anhydrous methanol–ether yields 8.8 g. (70% based on carbobenzoxyglycine); m.p. 140°.

Anal. Calcd. for $C_9H_{11}O_2N\cdot HCl$ (201.7): N, 7.0; HCl, 18.1. Found: N, 7.0; HCl, 18.1.

5. **L-Alanine Benzyl Ester Hydrochloride.**—Alanine carbamino anhydride[17] is obtained more easily than the corresponding glycine derivative. Following the method of Hunt and du Vigneaud[18] with minor changes (stirring, etc.), 22 g. (0.1 mole) of carbobenzoxy-L-alanine[16] is treated with 25 g. (0.12 mole) of PCl_5. The carbobenzoxy-L-alanyl chloride is converted, at a bath temperature of 40–45°, into the well-crystallizing anhydride. After washing with petroleum ether, the anhydride is dissolved in 50 cc. of benzyl alcohol and added to 500 cc. of ether previously saturated with HCl at 0°. After standing at 25° overnight, 16 g. (m.p. 137–138°) of benzyl ester hydrochloride is obtained, which yields 15 g. on recrystallization from anhydrous methanol–ether (70% based on carbobenzoxyalanine); m.p. 140°; $[\alpha]^{25}D$ −10.9° (2% in 0.1 *N* HCl).

Anal. Calcd. for $C_{10}H_{13}O_2N\cdot HCl$ (215.7): N, 6.5; NH_2-N, 6.5; HCl, 16.9. Found: N, 6.5; NH_2-N, 6.5; HCl, 17.0.

6. **D-Alanine Benzyl Ester Hydrochloride.**—This compound is obtained from carbobenzoxy-D-alanine with the same procedure and yield as the L-isomer; m.p. 139–140°; $[\alpha]^{25}D$ +10.5° (2% in 0.1 *N* HCl).

Anal. Found: N, 6.6; NH_2-N, 6.5; HCl, 16.9.

Carbobenzoxydipeptide Esters (Compounds 7–16).—In a mixture of 60 cc. of glacial acetic acid, 24 cc. of 5 *N* HCl and 250 cc. of water, 0.05 mole of a carbobenzoxy amino acid hydrazide is dissolved and cooled to −5°. On adding in one portion a cold, concentrated, aqueous solution of sodium nitrite (0.053 mole), the azide precipitates as a sirup[19] and is taken up in 300 cc. of cold ether. The ether layer is kept cold while washing successively with water, 3% $NaHCO_3$, and again with water. After brief drying over sodium sulfate, the azide solution is added in one portion to a dry, cold, ethereal solution of an amino acid ester (previously prepared from 0.07 mole of the amino acid ester hydrochloride). After standing for about 20 hours at room temperature, the reaction mixture is washed successively with 0.5 *N* HCl, water, 3% $NaHCO_3$ and water; after drying over sodium sulfate and removing the ether *in vacuo*, crystalline products are obtained, which are recrystallized from ethyl acetate–petroleum ether; yield of pure compounds is 65–70% based on the hydrazide used.

Carbobenzoxy-dipeptide Hydrazides (Compounds 17–20).—For the preparation of a hydrazide, 0.05 mole of carbobenzoxy dipeptide ethyl ester is dissolved in 80–100 cc. of hot, absolute alcohol, 0.10–0.13 mole of hydrazine hydrate added, and the solution refluxed for one hour. After standing for about 20 hours at room temperature, most of the hydrazide has crystallized; only small amounts can be obtained from the mother liquor after cooling and addition of ether. Recrystallization from ethyl alcohol–ether yields 80–90% of pure carbobenzoxy dipeptide hydrazide.

Carbobenzoxy Dipeptides (Compounds 21–24).—The carbobenzoxy dipeptide ethyl esters are saponified in acetone–*N* NaOH (about 15–20% excess of NaOH) for about ½ hour. After addition of a slight excess of *N* HCl, the mixture is concentrated *in vacuo*. Compounds 21, 22 and 24 are recrystallized from ethyl acetate–petroleum ether, 23 from hot water. The yield of pure compounds is somewhat variable, 65–85%. The neutralization equivalent (neut. equiv.) is obtained by titration in alcohol.[20]

Dipeptides (Compounds 25–30).—Hydrogenolysis of of 0.02 mole of a carbobenzoxy dipeptide is carried out in about 100 cc. of methanol containing a few drops of acetic acid with palladium black as catalyst in a rapid stream of hydrogen. About 6 cc. of palladium black suspension (0.5 g. Pd) in the appropriate solvent is used per 0.01 mole of the group to be reduced (carbobenzoxy or benzyl). Water is added, if necessary, to keep the peptide in solution during hydrogenation. After about two hours the hydrogenation of carbobenzoxy dipeptides is complete, as indicated by cessation of CO_2 evolution. Carbobenzoxy dipeptide benzyl esters are then hydrogenated for an additional two hours. Concentration *in vacuo* of the filtrate and washings results in crystallization of the peptides, which are recrystallized from water-alcohol. The yield of pure peptides varies from 70 to 85%; it is larger in the case of the benzyl esters, where the yield may be as high as 95%.

This work was aided by a contract between the Office of Naval Research, Department of the Navy, and Columbia University (NR 122–260).

(17) The carbamino anhydrides (oxazolid-2,5-diones) of glycine and alanine were recently synthesized directly from the amino acids by treatment with carbonyl chloride by Farthing (*J. Chem. Soc.*, 3213 (1950)). This author, incidentally, states that preparation of benzyl chloroformate according to Bergmann,[16] using a toluene solution of carbonyl chloride, gave colored crude products. Such reports from the United Kingdom have come to our attention previously. However, investigators in this country have no trouble in obtaining colorless pure benzyl chloroformate by Bergmann's method. The reason for this discrepancy remains unexplained.

(18) Hunt and du Vigneaud, *J. Biol. Chem.*, **124**, 699 (1938).

(19) Carbobenzoxyglycine azide is crystalline.

(20) Ellenbogen and Brand, Am. Chem. Soc., Philadelphia Meeting, April 1950, Abstracts p. 56-C.

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Optical Rotation of Peptides. II. Glycine and Alanine Tripeptides[1]

BY ERWIN BRAND, BERNARD F. ERLANGER, HOWARD SACHS AND JEROME POLATNICK

The first paper in this series dealt with the synthesis and specific rotation of dipeptides of alanine.[2] In this paper the syntheses and specific rotations (in 0.5 *N* HCl) of nine glycine and alanine tripeptides are presented. More detailed data on their specific rotations and on the *residue rotations*[3] of alanine residues will be reported subsequently.

Experimental

The synthesis and properties of most of the starting materials have been previously described[2]: L- and D-alanine, benzyl esters of glycine and of L- and D-alanine (ref. 2, Compounds 4–6), four isomeric carbobenzoxy-alanyl-alanine hydrazides (ref. 2, Compounds 17–20). Carbobenzoxy-glycyl-L-alanine hydrazide and its D-isomer were prepared according to Bergmann.[4]

Carbobenzoxy Tripeptide Esters (Compounds 1–13).—The coupling of the azides of carbobenzoxy dipeptide hydrazides (0.025 mole) with amino acid esters (0.0375 mole) is carried out as described in detail for the synthesis of dipeptide esters[2] with the following changes: only 0.025 mole of a carbobenzoxy dipeptide hydrazide is dissolved in the

(1) Presented in part before the Division of Biological Chemistry at the 118th Meeting of the A. C. S., Chicago, Ill., September, 1950.

(2) Erlanger and Brand, THIS JOURNAL, **73**, 3508 (1951).

(3) Brand and Erlanger, *ibid.*, **72**, 3314 (1950).

(4) Bergmann and Zervas, *J. Biol. Chem.*, **113**, 341 (1936).