bath for 2–3 hr. The amine hydrochloride was filtered and the solvent distilled at reduced pressure. The product, if a liquid, was vacuum distilled; if a solid, it was recrystallized from the appropriate solvent.

**5,5,5-Trichloro-2-pentenyl Carbamates.**—5,5,5-Trichloro-2-pentenyl N-butylcarbamate (XXXVI), 5,5,5-trichloro-2-pentenyl N-propylcarbamate (XXXVII), 5,5,5-trichloro-2-pentenyl N-(1-methylpropyl) carbamate (XXXVIII), and 5,5,5-trichloro-2-pentenyl N-phenylcarbamate (XXXIX) were prepared by the method outlined (see Table IV).

Approximately 50 g. of the isocyanate was added dropwise to 0.370 mole of XXXI. After all the isocyanate had been added, the solution was heated on a hot water bath for 1 hr. and finally at 110° for 4 hr. The mixture was then vacuum distilled and the product isolated. If the carbamate was a solid it was recrystallized from the appropriate solvent.

**5,5,5-Trichloro-2-pentenyl Carbanilates.**—5,5,5-Trichloro-2-pentenyl 2-chlorocarbanilate (XLVI), 5,5,5-trichloro-2-pentenyl 2,4-dichlorocarbanilate (XLVII), and 5,5,5-trichloro-2-pentenyl 2,4,6-trichlorocarbanilate (XLVIII) were prepared by the method outlined (see Table IV).

Approximately 0.200 mole of the amine was dissolved in 50 ml. of acetone. To this solution was added dropwise 0.1 mole of the chloroformate XLI. After all the chloroformate had been added, the solution was refluxed for 2 hr. The amine hydrochloride was filtered and washed with acetone. The acetone was distilled and the residue extracted with water. The organic layer was separated and the aqueous layer extracted with chloroform. The combined crude carbanilate and chloroform solution was dried over magnesium sulfate, filtered, and the solvent removed under reduced pressure. An attempt to vacuum distill a small portion of the liquid carbamates resulted in decomposition. The last traces of solvent were removed with a high vacuum pump. The solid carbanilates were recrystallized from appropriate solvents.

**5,5,5-Trichloro-2-pentenyl Ester of the Anhydrosulfide of Thiol Carbonic Acid and O,O-Diethyl Phosphorodithioic Acid (XLIX).**—Ammonium O,O-diethyl phosphorodithioate, 41 g. (0.2 mole), was dissolved in 175 ml. of acetone. To this solution was added dropwise 50.4 g. (0.20 mole) of the chloroformate XLI. The temperature of the reaction rose slowly from 24° to a maximum of 35°. After all the chloroformate had been added, the solution was heated on a water bath for 2 hr. After cooling, the solid was filtered and washed with acetone. The acetone was distilled at reduced pressure and the last traces of solvent removed with a vacuum pump. The crude product weighed 61 g. (76%).

*Anal.* Calcd. for $C_{10}H_{16}Cl_3O_4PS_2$: C, 30.00; H, 4.00; P, 7.50. Found: C, 29.97; H, 4.05; P, 8.10.

**5,5,5-Trichloro-2-pentenyl Allophanate (L).**—Following the procedure of Dains,[10] *et al.*, XLI, 25.2 g. (0.1 mole) was added to 12.6 g. (0.21 mole) of urea. This mixture was heated on a water bath for 3 hr. The solid isolated was washed with water and then with heptane. The crude solid was recrystallized from methanol; the product 12 g. (44%), melted at 182–183°.[11]

*Anal.* Calcd. for $C_7H_9Cl_3N_2O_3$: C, 30.40; H, 3.26. Found: C, 30.42; H, 3.25.

(10) F. B. Dains and E. Wertheim, *J. Am. Chem. Soc.*, **42**, 2303 (1920).

(11) All melting points are uncorrected. Elemental and infrared analyses by Diamond Alkali Co. Research Analytical Laboratory.

# The Preparation of Succinamido Peptides[1]

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The introduction of cystine as a linkage in polypeptidic structures is not without difficulties. Assuming that, in a number of cases where cystine is present in the natural peptide, it plays no specific pharmacodynamic role, some other residue might well be able to replace cystine, without altering the characteristic activity of the peptide. Succinic acid seemed particularly attractive as a replacement for cystine. The present paper describes the preparation of symmetric and mixed succinamido peptides. The method may well be capable of being extended to the preparation of more complex structures, which are perhaps biologically interchangeable with natural cystine.

Compounds where a dicarboxylic acid is linked with two amino acids through their amino groups, or compounds where a diamine is linked to two amino acids through their carboxylic groups are known in nature. Such a combination offers a wide range of possibilities from the point of view of synthesis. However, it appears that only a few such compounds have been described in the literature, *e.g.*, the derivatives of oxalic, succinic, and adipic acids.[2-8] The recent publication of Schröder, Klieger, and Gibian[9] reports more syntheses of this class of compounds. In addition, a number of succinimides have been synthesized: *e.g.* succinimidoglycine,[6,10] succinimido-DL-alanine,[6] succinimido-L-leucine,[6] and succinimido-L-valine.[6] Also a number of β-carboxypropionylamino acids have been synthesized, for example β-carboxypropionylglycine, β-carboxypropionyl-L-leucine, and β-carboxypropionyl-DL-alanine.[6]

We have been particularly interested in the preparation of compounds where the two carboxylic groups of succinic acid are linked to the basic

(1) This paper was presented in abridged form at the 26th and 28th Meeting of l'ACFAS at Ottawa (Canada), October 31, November 1–2, 1958, and at Quebec (Canada), October 27–30, 1960, respectively.

(2) J. Th. Bornauter, *Rec. trav. chim.*, **31**, 105 (1912).

(3) H. Schiff, *Ber.*, **18**, 490 (1885).

(4) D. J. Meijeringh, *Rec. trav. chim.*, **32**, 146 (1913).

(5) Th. Curtius, *J. prakt. Chem.* [2], **91**, 21 (1915); [2], **105**, 302 (1922).

(6) C. Berse, dissertation, E.T.H. Zürich (Switzerland), 1947.

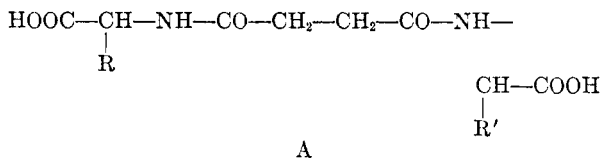
(7) W. R. Hearn and R. A. Hendry, *J. Am. Chem. Soc.*, **79**, 5213 (1957).

(8) G. Faust and M. Klepel, *J. prakt. Chem.* [4], **11**, 133 (1960).

(9) E. Schröder, E. Klieger, and H. Gibian, *Ann.*, **646**, 101 (1961).

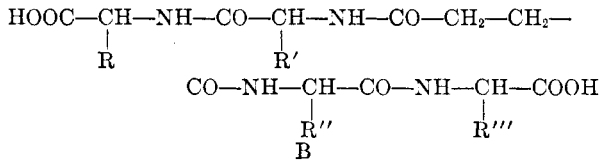
(10) J. Scheiber and H. Reckleben, *Ber.*, **46**, 2415 (1913).

function of amino acids, A, or dipeptides, B, whereby symmetrical as well as mixed derivatives of the following general formulas may be obtained:



A

R = $R^1$ in the case of mixed compounds



B

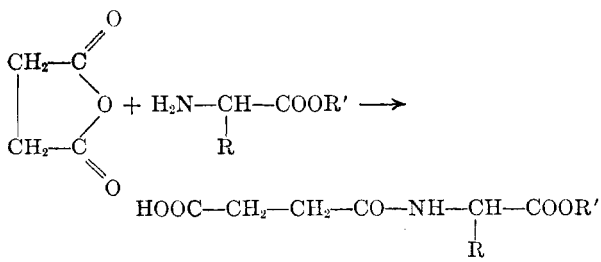
By varying R, R′, R″, R‴ in the dipeptide one obtains symmetrical or mixed diamides of succinic acid.

We attempted to prepare the symmetrical succinamides by the mixed anhydride[11] and by the carbodiimide[12] method. This was unsuccessful.

We decided therefore to use the acid chloride procedure, and in particular the modified preparation of Vorländer.[13] In this modification the acid chloride is prepared by heating succinic anhydride with phosphorus pentachloride. To carry out the condensation reactions, we used amino acid esters in organic solvents. This approach yields neutral succinamides, which facilitated the purification of the condensation products.

There is no adequate procedure to synthesize mixed succinamides in one step. At present, such a synthesis requires, first the preparation of monosuccinamides of the amino acids or of the peptide, as was demonstrated by Meijeringh[4] in his synthesis of the oxalic diamides of mixed amino acids.

In this work one mole of succinic anhydride was brought into reaction with one mole of the amino acid ester or peptide ester to form a monoamide of succinic acid. The intermediate compound bears a



free carboxylic function which can be condensed with the second amino acid ester or a peptide ester. A mixed succinic diamide is thus formed. This second condensation was carried out using the mixed anhydride method.[11]

(11) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

(12) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).

(13) D. Vorländer, *Ann.*, **280**, 183 (1894).

## Experimental[14,15]

**Succinylbis(DL-phenylalanine Ethyl Ester)** (I).—Ethyl DL-phenylalanate hydrochloride[16] (2.30 g., 0.01 mole) was dissolved in 50 ml. of dioxane and 4.8 ml. of tri-*n*-butylamine was added. The solution was stirred vigorously and cooled to −10°. A solution of succinyl chloride (0.78 g., 0.005 mole) in 20 ml. of dioxane was added dropwise. Stirring was continued for 2 hr. at room temperature and the solvent was evaporated *in vacuo*. The residue was dissolved in ethyl acetate and this solution was washed with *N* hydrochloric acid, water, 5% aqueous bicarbonate, and water, then dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the residue was recrystallized from toluene–petroleum ether; yield 1.24 g. (55%), m.p. 146–147°.

*Anal.* Calcd. for $C_{26}H_{32}N_2O_6$: C, 66.65; H, 6.88; N, 6.11. Found: C, 66.67; H, 6.85; N, 6.02.

**Succinylbis(DL-phenylalanine)** (II).—Succinylbis(DL-phenylalanine ethyl ester) (1.17 g. 0.0025 mole) was dissolved in dioxane (25 ml.); *N* sodium hydroxide (5.5 ml.) was added, and the mixture was stirred for 2 hr. at room temperature. The alkaline solution was washed with ethyl acetate and acidified to Congo red with 4 *N* hydrochloric acid. The product crystallized after a few hours; for recrystallization the product was dissolved in cold N,N-dimethylformamide and precipitated with water; yield 0.849 g. (83%), m.p. 246–247°.

Neut. equiv.: Weight of sample: 210 mg. Volume of alkali: 10.18 ml. of 0.0994 *N* NaOH. Mol. wt. Calcd. 412.4. Found. 415.2.

*Anal.* Calcd. for $C_{22}H_{24}N_2O_6$: C, 64.06; H, 5.87; N, 6.79. Found: C, 64.14; H, 5.85; N, 6.83.

**Succinylbis(L-phenylalanine Methyl Ester)** (III).—This compound was prepared by the procedure for I. Methyl-L-phenylalanate hydrochloride[17] (2.157 g., 0.01 mole) reacted with succinyl chloride (0.78 g., 0.005 mole) in the presence of tributylamine (4.8 ml.); yield 1.17 g. (53%), m.p. 133–134°, $[\alpha]^{25}D$ −13.4 (*c*, 0.76 in ethanol).

*Anal.* Calcd. for $C_{24}H_{28}N_2O_6$: C, 65.44; H, 6.40; N, 6.36. Found: C, 65.42; H, 6.36; N, 6.50.

**Succinylbis(L-phenylalanine)** (IV).—Succinylbis(L-phenylalanine methyl ester) (1.10 g. 2.5 mmoles) was saponified by the procedure for II; yield 0.742 g. (72%), m.p. 209–210°, $[\alpha]^{25}D$ +22.2 (*c*, 0.27 in dimethylformamide).

Neut. equiv.: Weight of sample: 250 mg. Volume of alkali: 12.37 ml. of 0.0094 *N* NaOH. Mol. wt. Calcd.: 412.4. Found: 410.0.

*Anal.* Calcd. for $C_{22}H_{24}N_2O_6$: C, 64.06; H, 5.87; N, 6.79. Found: C, 63.99; H, 5.88; N, 6.85.

**Succinylbis(L-glutamic Acid Diethyl Ester)** (V).—This compound was prepared by the procedure for I. L-Glutamic acid diethyl ester hydrochloride[18] (2.39 g., 0.01 mole) reacted with succinyl chloride (0.78 g., 0.005 mole) in the presence of tributylamine. The product was recrystallized from ethyl acetate–petroleum ether; yield 53%, m.p. 57–58°, $[\alpha]^{25}D$ −24.9 (*c*, 1.6 in ethanol).

*Anal.* Calcd. for $C_{22}H_{36}N_2O_{10}$: C, 54.08; H, 7.42; N, 5.73. Found: C, 54.09; H, 7.44; N, 5.88.

**Succinylbis(L-glutamic Acid Dibenzyl Ester)** (VI).—This compound was prepared by the procedure for I. L-Glutamic acid dibenzyl ester hydrochloride[19] (3.63 g., 0.01 mole) was condensed with succinyl chloride (0.78 g., 0.005 mole) in dioxane in the presence of triethylamine. The

(14) Melting points, unless otherwise indicated, have been determinated in semicapillary tubes and are uncorrected.

(15) Microanalyses were determined by W. Manser, Zurich (Switzerland).

(16) Th. Curtius and E. Müller, *Ber.*, **37**, 1266 (1904).

(17) R. A. Boissonnas, St. Guttmann, P.-A. Jaquenoud, and J.-P. Waller, *Helv. Chim. Acta*, **39**, 1421 (1956).

(18) F. Knoop and H. Oesterlin, *Z. physiol. Chem.*, **170**, 204 (1929).

(19) H. Sachs and E. Brand, *J. Am. Chem. Soc.*, **75**, 4610 (1953).

product was recrystallized first from ethanol–petroleum ether and then from carbon tetrachloride–petroleum ether and then from carbon tetrachloride–petroleum ether; yield 59%, m.p. 108–109°, $[\alpha]^{25}D$ −10.3 (*c*, 0.1 in ethanol).

*Anal.* Calcd. for $C_{42}H_{44}O_{10}N_2$: C, 68.47; H, 6.02; N, 3.80. Found: C, 68.36; H, 6.07; N, 3.69.

**Succinylbis(L-glutamic Acid) (VII).**—Succinylbis(L-glutamic acid dibenzyl ester) (0.736 g., 1.0 mmole) was dissolved in methanol. The compound was hydrogenated for 1 hr. at room temperature and at atmospheric pressure over 10% palladium on carbon (500 mg.). After filtration, the catalyst was washed with hot methanol, and the washings were combined with the first filtrate. The solvent was evaporated *in vacuo* and the residue crystallized from methanol–ether; $[\alpha]^{26}D$ −2.8 (*c*, 0.18 in ethanol), yield 0.30 g. (80%), m.p. 143–135°.

*Anal.* Calcd. for $C_{14}H_{20}N_2O_{10}$: C, 44.68; H, 5.36; N, 7.44. Found: C, 44.63; H, 5.50; N, 7.49.

**Succinylbis(ω-nitro-L-arginine Methyl Ester) (VIII).**—Methyl ω-nitro-L-arginate hydrochloride[20] (6.20 g., 0.023 mole) was dissolved in hot methanol (30 ml.). Triethylamine (3.18 ml.) was added, and the mixture was allowed to stand at room temperature for 10 min. The solvent was evaporated *in vacuo*. The residue, a thick oil, was dissolved in a mixture of dioxane and N,N-dimethylformamide (50:50) and triethylamine (3.18 ml.) was added. The mixture was cooled with an ice–salt mixture and succinylchloride (1.765 g., 0.0114 mole), dissolved in dioxane (25 ml.), was added dropwise. The mixture was stirred for 2 hr. at room temperature, then the triethylamine hydrochloride was filtered and the solvent evaporated *in vacuo*. The residue, an oil, was dissolved in water. The aqueous solution was passed first through Amberlite IR-45 (25 ml.). The Amberlite IR-45 was previously washed with *N* hydrochloric acid (250 ml.), water, *N* sodium hydroxide (300 ml.), water (a few liters). The second time the product was passed through Amberlite XE-100 (50 ml.), which previously was washed with *N* sodium hydroxide (250 ml.) water, *N* hydrochloric acid (300 ml.), water (a few liters). After passing of the aqueous solution of the compound through both resins, the water was evaporated *in vacuo*. The residue, an oil, was dissolved in propanol–ethanol (60:40) and the solid product was precipitated by the addition of ether; yield 3.55 g. (55%), m.p. 106–107°, $[\alpha]^{25}D$ +2.4 (*c*, 1.1 in methanol).

*Anal.* Calcd. for $C_{18}H_{32}N_{10}O_{10}$: C, 39.41; H, 5.88; N, 25.54. Found: C, 39.45; H, 5.85; N, 25.47.

**Siccinylbis(ω-nitro-L-arginine) (IX).**—Succinylbis(ω-nitro-L-arginine methyl ester) (548 mg., 1.0 mmole) was stirred for 2 hr. at room temperature with *N* sodium hydroxide (31 ml.). The alkaline solution was acidified with *N* hydrochloric acid until it was weakly acidic. Then the water was evaporated *in vacuo* to dryness. The residue was dissolved in hot propanol, then insoluble sodium chloride was filtered. The product was crystallized by the addition of ether; yield 493 mg. (88%), m.p. 141–142°, $[\alpha]^{25}D$ −0.4 (*c*, 1.6 in dimethylformamide).

Neut. equiv.: Weight of sample: 47.2 mg. Volume of alkali: 1.8 ml. of 0.0974 *N* NaOH. Mol. wt. Calcd.: 520.5. Found: 538.4.

*Anal.* Calcd. for $C_{18}H_{28}N_{10}O_{10}$: C, 36.92; H, 5.42; N, 26.91. Found: C, 36.85; H, 5.46; N, 27.01.

**Succinylbis(O-benzyl-L-tyrosine Methyl Ester) (X).**—Methyl O-benzyl-L-tyrosinate hydrochloride[21] (3.69 g., 0.0115 mole) was dissolved in dimethylformamide (25 ml.). Triethylamine (2.72 ml.) in dioxane (25 ml.) was added. After cooling of the solution to 10°, succinyl chloride (891 mg., 5.75 mmoles) in dioxane (25 ml.) was added, and the mixture was stirred at this temperature for 30 min., then for 2 hr. at room temperature. Triethylamine hydrochloride was filtered and the solvent evaporated *in vacuo*. The residue was dissolved in ethyl acetate and the solution washed with *N* hydrochloric acid, water, *N* sodium bicarbonate, and water. After drying over anhydrous sodium sulfate the solvent was concentrated *in vacuo*. The product was recrystallized from ethyl acetate–petroleum ether; yield 1.87 g. (59%), m.p. 159–161°, $[\alpha]^{25}D$ +61.1 (*c*, 0.36 in tetrahydrofuran).

*Anal.* Calcd. for $C_{38}H_{40}N_2O_8$: C, 69.92; H, 6.18; N, 4.29. Found: C, 69.74; H, 6.34; N, 4.22.

**Succinylbis(L-tyrosine Methyl Ester) (XI).**—Succinylbis(O-benzyl-L-tyrosine methyl ester) (3.21 g. 5.0 mmoles) was dissolved in acetone (20 ml.). The compound was hydrogenated for 12 hr. at room temperature and atmospheric pressure over 10% palladium on carbon (1.5 g.). The catalyst was removed by filtration and the filtrate evaporated *in vacuo*. The compound was dissolved in methanol and crystallized by the addition of petroleum ether; yield 2.0 g. (84%), m.p. 154–155°, $[\alpha]^{25}D$ +19.26 (*c*, 1.26 in ethanol).

*Anal.* Calcd. for $C_{24}H_{28}N_2O_8$: C, 61.01; H, 5.93; N, 5.93. Found: C, 60.95; H, 6.00; N, 5.86.

**Ethyl β-Carboxypropionylglycinate (XII).**—Succinic anhydride (10 g., 0.1 mole) was dissolved in chloroform (50 ml.) and glycine ethyl ester (10.3 g., 0.1 mole) in chloroform (50 ml.) was added. The reaction was vigorous and after standing for 4 hr. at room temperature the product crystallized. The product was recrystallized from chloroform–ether; yield 17.2 g. (85%), m.p. 96–97°.

*Anal.* Calcd. for $C_8H_{13}NO_5$: C, 47.29; H, 6.45; N, 6.89. Found: C, 47.32; H, 6.51; N, 6.98.

**Succinyl(glycine Ethyl Ester, DL-Phenylalanine Ethyl Ester) (XIII).**—Ethyl (β-carboxypropionyl)glycinate (1.015 g. 5.0 mmoles) was dissolved in dioxane (50 ml.) and tributylamine (1.20 ml.) was added. After cooling with an ice–salt mixture, ethyl chloroformate (0.48 ml.) was added. The mixture was stirred for 15 min. After this, a solution of DL-phenylalanine ethyl ester hydrochloride (1.15 g., 0.005 mole) of tributylamine (1.2 ml.) in dioxane (50 ml.) was added. The mixture was stirred for 5 hr. at room temperature then the solvent was evaporated *in vacuo* at 50–60°. The residue was dissolved in ethyl acetate (50 ml.) and this solution was washed with *N* hydrochloric acid, water, 5% aqueous bicarbonate, and water. The solvent was concentrated *in vacuo* and the product crystallized by the addition of petroleum ether; yield 1.50 g. (80%), m.p. 101–102°.

*Anal.* Calcd. for $C_{19}H_{26}N_2O_6$: C, 60.30; H, 6.93; N, 7.40. Found: C, 60.31; H, 6.91; N, 7.43.

**Succinyl(glycine, DL-Phenylalanine) (XIV).**—Succinyl(glycine ethyl ester, DL-phenylalanine ethyl ester) (2.27 g., 3.0 mmoles) was dissolved in ethanol, *N* sodium hydroxide (7 ml.) was added, and the mixture stirred for 2 hr. at room temperature. The alkaline solution was washed with ethyl acetate, acidified with *N* hydrochloric acid to Congo red, and the solvent was evaporated *in vacuo* to dryness. The residue was dissolved in absolute ethanol and again evaporated *in vacuo;* then the product was dissolved in tetrahydrofuran and the insoluble sodium chloride filtered. The compound crystallized on the addition of ether at 0°; yield 885 mg. (82%), m.p. 191–193°.

*Anal.* Calcd. for $C_{15}H_{18}N_2O_6$: C, 55.86; H, 5.63; N, 8.69. Found: C, 55.82; H, 5.66; N, 8.89.

**Succinyl(glycine Ethyl Ester, L-Phenylalanine Methyl Ester) (XV).**—This compound was prepared by the procedure for XIII. Methyl L-phenylalanate hydrochloride (1.08 g. 5 mmoles) was combined with ethyl β-carboxypropionylglycinate (1.02 g. 5 mmoles); yield 1.7 g. (86%), m.p. 92–93°, $[\alpha]^{26}D$ +12.7 (*c*, 1.4 in methanol).

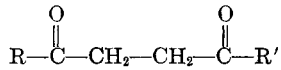
*Anal.* Calcd. for $C_{18}H_{24}N_2O_6$: C, 58.32; H, 6.64; N, 7.69. Found: C, 59.32; H, 6.60; N, 7.69.

**Succinyl(glycine, L-Phenylalanine) (XVI).**—Saponification of the corresponding diester (960 mg. 2.5 mmoles) was effected by the procedure for XIV with *N* sodium hydroxide

(20) H. O. Van Orden and E. L. Smith, *J. Biol. Chem.*, **208**, 751 (1954).

(21) E. Hünsch, G. Fries, and A. Zwick, *Ber.*, **91**, 542 (1958).

TABLE I



| No. | Name | R |
|---|---|---|
| I | Succinylbis(DL-phenylalanine ethyl ester) | —NHCH($CH_2C_6H_5$)$COOC_2H_5$ |
| II | Succinylbis(DL-phenylalanine) | —NHCH($CH_2C_6H_5$)COOH |
| III | Succinylbis(L-phenylalanine methyl ester) | —NHCH($CH_2C_6H_5$)$COOCH_3$ |
| IV | Succinylbis(L-phenylalanine) | —NHCH($CH_2C_6H_5$)COOH |
| V | Succinylbis(L-glutamic acid diethyl ester) | – NHCH($CH_2CH_2COOC_2H_5$)$COOC_2H_5$ |
| VI | Succinylbis(L-glutamic acid dibenzyl ester) | —NHCH($CH_2CH_2COOCH_2C_6H_5$)$COOCH_2C_6H_5$ |
| VII | Succinylbis(L-glutamic acid) | —NHCH($CH_2CH_2COOH$)COOH |
| VIII | Succinylbis(ω-nitro-L-arginine methyl ester) | —NHCH[$(CH_2)_3NHC(=NH)NHNO_2$]$COOCH_3$ |
| IX | Succinylbis(ω-nitro-L-arginine) | —NHCH[$(CH_2)_3NHC(=NH)NHNO_2$]COOH |
| X | Succinylbis(*O*-benzyl-L-tyrosine methyl ester) | —NHCH($CH_2C_6H_4OCH_2C_6H_5$)$COOCH_3$ |
| XI | Succinylbis(L-tyrosine methyl ester) | —NHCH($CH_2C_6H_4OH$)$COOCH_3$ |
| XII | Ethyl β-carboxypropionylglycinate | —$NHCH_2COOC_2H_5$ |
| XIII | Succinyl(glycine ethyl ester, DL-phenylalanine ethyl ester) | —$NHCH_2COOC_2H_5$ |
| XIV | Succinyl(glycine, DL-phenylalanine) | —$NHCH_2COOH$ |
| XV | Succinyl(glycine ethyl ester, L-phenylalanine methyl ester) | —$NHCH_2COOC_2H_5$ |
| XVI | Succinyl(glycine, L-phenylalanine) | —$NHCH_2COOH$ |
| XVII | Succinyl(glycine ethyl ester, L-glutamic acid diethyl ester) | —$NHCH_2COOC_2H_5$ |
| XVIII | Ethyl β-carboxypropionyl-DL-phenylalanate | —NHCH($CH_2C_6H_5$)$COOC_2H_5$ |
| XIX | Succinyl(DL-phenylalanine ethyl ester, L-glutamic acid diethyl ester) | —NHCH($CH_2C_6H_5$)$COOC_2H_5$ |
| XX | Succinyl(DL-phenylalanine ethyl ester, ω-nitro-L-arginine methyl ester) | —NHCH($CH_2C_6H_5$)$COOC_2H_5$ |
| XXI | Ethyl β-carboxypropionyl-L-phenylalanate | —NHCH($CH_2C_6H_5$)$COOC_2H_5$ |
| XXII | Succinyl(L-phenylalanine ethyl ester, ω-nitro-L-arginine methyl ester) | —NHCH($CH_2C_6H_5$)$COOC_2H_5$ |
| XXIII | Methyl β-carboxypropionyl-*O*-benzyl-L-tyrosinate | —NHCH($CH_2C_6H_4OCH_2C_6H_5$)$COOCH_3$ |
| XXVII | Succinylbis(glycyl-L-phenylalanine ethyl ester) | —$NHCH_2CONHCH(CH_2C_6H_5)COOC_2H_5$ |
| XXVIII | Succinylbis(glycyl-L-phenylalanine) | —$NHCH_2CONHCH(CH_2C_6H_5)COOH$ |
| XXXI | Succinylbis(glycyl-L-leucine ethyl ester) | —$NHCH_2CONHCH[CH_2CH(CH_3)_2]COOC_2H_5$ |
| XXXII | Succinylbis(glycyl-L-leucine) | —$NHCH_2CONHCH[CH_2CH(CH_3)_2]COOH$ |
| XXXIII | Ethyl β-carboxypropionylglycyl-L-phenylalanate | —$NH_2CH_2CONHCH(CH_2C_6H_5)COOC_2H_5$ |
| XXXIV | Succinyl(glycyl-L-phenylalanine ethyl ester, glycyl-L-leucine ethyl ester) | —$NHCH_2CONHCH(CH_2C_6H_5)COOC_2H_5$ |

TABLE I (*continued*)

| R′ | M.p., °C. | $[\alpha]^{25}D$ | Formula | | % C | % H | % N |
|---|---|---|---|---|---|---|---|
| —NHCH($CH_2C_6H_5$)$COOC_2H_5$ | 146–147 | ... | $C_{26}H_{32}N_2O_6$ | Calcd. | 66.65 | 6.88 | 6.11 |
| | | | | Found | 66.67 | 6.85 | 6.02 |
| —NHCH($CH_2C_6H_5$)COOH | 246–247 | ... | $C_{22}H_{24}N_2O_6$ | Calcd. | 64.06 | 5.87 | 6.79 |
| | | | | Found | 64.14 | 5.85 | 6.83 |
| —NHCH($CH_2C_6H_5$)$COOCH_3$ | 133–134 | −13.4 (*c*, 0.76 in ethanol) | $C_{24}H_{28}N_2O_6$ | Calcd. | 65.44 | 6.40 | 6.36 |
| | | | | Found | 65.42 | 6.36 | 6.50 |
| —NHCH($CH_2C_6H_5$)COOH | 209–210 | +22.2 (*c*, 0.27 in dimethylformamide) | $C_{22}H_{24}N_2O_6$ | Calcd. | 64.06 | 5.87 | 6.79 |
| | | | | Found | 63.99 | 5.88 | 6.85 |
| —NHCH($CH_2CH_2COOC_2H_5$)$COOC_2H_5$ | 57–58 | −24.9 (*c*, 1.6 in ethanol) | $C_{22}H_{36}N_2O_{10}$ | Calcd. | 54.08 | 7.42 | 5.73 |
| | | | | Found | 54.09 | 7.44 | 5.88 |
| —NHCH($CH_2CH_2COOCH_2C_6H_5$)-$COOCH_2C_6H_5$ | 108–109 | +10.3 (*c*, 0.1 in ethanol) | $C_{42}H_{44}N_2O_{10}$ | Calcd. | 68.47 | 6.02 | 3.80 |
| | | | | Found | 68.36 | 6.07 | 3.69 |
| —NHCH($CH_2CH_2COOH$)COOH | 143–145 | −2.8 (*c*, 0.18 in ethanol) | $C_{14}H_{20}N_2O_{10}$ | Calcd. | 44.68 | 5.36 | 7.44 |
| | | | | Found | 44.63 | 5.50 | 7.49 |
| —NHCH[$(CH_2)_3NHC(=NH)NHNO_2$]$COOCH_3$ | 106–107 | +2.4 (*c*, 1.1 methanol) | $C_{18}H_{32}N_{10}O_{10}$ | Calcd. | 39.41 | 5.88 | 25.54 |
| | | | | Found | 39.45 | 5.85 | 25.47 |
| —NHCH[$(CH_2)_3NHC(=NH)NHNO_2$]COOH | 141–142 | −0.4 (*c*, 1.6 in dimethylformamide) | $C_{16}H_{28}N_{10}O_{10}$ | Calcd. | 36.92 | 5.42 | 26.91 |
| | | | | Found | 36.85 | 5.46 | 27.01 |
| —NHCH($CH_2C_6H_4OCH_2C_6H_5$)$COOCH_3$ | 159–161 | +61.1 (*c*, 0.36 in tetrahydrofurane) | $C_{36}H_{40}N_2O_8$ | Calcd. | 69.92 | 6.18 | 4.29 |
| | | | | Found | 69.74 | 6.34 | 4.22 |
| —NHCH($CH_2C_6H_4OH$)$COOCH_3$ | 154–155 | +19.26 (*c*, 1.26 in ethanol) | $C_{24}H_{28}N_2O_8$ | Calcd. | 61.01 | 5.93 | 5.93 |
| | | | | Found | 60.95 | 6.00 | 5.86 |
| —OH | 96–97 | ... | $C_8H_{13}NO_5$ | Calcd. | 47.29 | 6.45 | 6.89 |
| | | | | Found | 47.32 | 6.51 | 6.98 |
| —NHCH($CH_2C_6H_5$)$COOC_2H_5$ | 101–102 | ... | $C_{19}H_{26}N_2O_6$ | Calcd. | 60.30 | 6.93 | 7.40 |
| | | | | Found | 60.31 | 6.91 | 7.43 |
| —NHCH($CH_2C_6H_5$)COOH | 191–193 | ... | $C_{15}H_{18}N_2O_6$ | Calcd. | 55.86 | 5.63 | 8.69 |
| | | | | Found | 55.82 | 5.66 | 8.89 |
| —NHCH($CH_2C_6H_5$)$COOCH_3$ | 92–93 | +12.7 (*c*, 1.4 in methanol) | $C_{18}H_{24}N_2O_6$ | Calcd. | 59.32 | 6.64 | 7.69 |
| | | | | Found | 59.32 | 6.60 | 7.69 |
| —NHCH($CH_2C_6H_5$)COOH | 149–150 | +23.1 (*c*, 1.21 in ethanol) | $C_{15}H_{18}N_2O_6$ | Calcd. | 55.86 | 5.63 | 8.69 |
| | | | | Found | 55.61 | 5.58 | 8.54 |
| —NHCH($CH_2CH_2COOC_2H_5$)$COOC_2H_5$ | 96–97 | −14.0 (*c*, 1.18 in methanol) | $C_{17}H_{28}N_2O_8$ | Calcd. | 52.56 | 7.269 | 7.21 |
| | | | | Found | 52.57 | 7.24 | 7.26 |
| —OH | 103–104 | ... | $C_{15}H_{19}NO_5$ | Calcd. | 61.42 | 6.53 | 4.77 |
| | | | | Found | 61.29 | 6.68 | 4.83 |
| —NHCH($CH_2CH_2COOC_2H_5$)$COOC_2H_5$ | 83–84 | +8.3 (*c*, 0.7 in ethanol) | $C_{24}H_{34}N_2O_8$ | Calcd. | 60.23 | 7.16 | 5.85 |
| | | | | Found | 59.94 | 6.87 | 5.82 |
| —NHCH[$(CH_2)_3NHC(=NH)NHNO_2$]$COOCH_3$ | 114–116 | −1.8 (*c*, 1.0 in methanol) | $C_{22}H_{32}N_6O_8$ | Calcd. | 51.96 | 6.34 | 16.53 |
| | | | | Found | 51.84 | 6.37 | 16.34 |
| —OH | 83–84 | +17.7 (*c*, 1.0 in methanol) | $C_{15}H_{19}NO_5$ | Calcd. | 61.42 | 6.53 | 4.77 |
| | | | | Found | 61.39 | 6.54 | 4.81 |
| —NHCH[$(CH_2)_3NHC(=NH)NHNO_2$]$COOCH_3$ | 124–126 | −5.0 (*c*, 1.6 in methanol) | $C_{22}H_{32}N_6O_8$ | Calcd. | 51.96 | 6.34 | 16.53 |
| | | | | Found | 51.96 | 6.49 | 16.63 |
| —OH | 85–86 | +23.14 (*c*, 1.08 in ethanol) | $C_{21}H_{23}NO_6$ | Calcd. | 65.44 | 6.01 | 3.63 |
| | | | | Found | 65.31 | 5.96 | 3.57 |
| —$NHCH_2CONHCH(CH_2C_6H_5)COOC_2H_5$ | 90 | +2.1 (*c*, 2.1 in ethanol) | $C_{30}H_{38}N_4O_8$ | Calcd. | 61.88 | 6.58 | 9.71 |
| | | | | Found | 61.07 | 6.66 | 9.99 |
| —$NHCH_2CONHCH(CH_2C_6H_5)COOH$ | 138–140 | +28.0 (*c*, 1.0 in 1 *N* NaOH) | $C_{26}H_{30}N_4O_8$ | Calcd. | 59.35 | 5.74 | 10.65 |
| | | | | Found | 58.98 | 5.97 | 10.53 |
| —$NHCH_2CONHCH[CH_2CH(CH_3)_2]$-$COOC_2H_5$ | 114 | −34.2 (*c*, 2.0 in ethanol) | $C_{24}H_{42}N_4O_8$ | Calcd. | 56.12 | 8.24 | 10.89 |
| | | | | Found | 56.18 | 8.26 | 10.78 |
| —$NHCH_2CONHCH[CH_2CH(CH_3)_2]$-COOH | 124 | −23.5 (*c*, 0.9 in 1 *N* NaOH) | $C_{20}H_{34}N_4O_8$ | Calcd. | 52.38 | 7.47 | 12.22 |
| | | | | Found | 52.49 | 7.40 | 12.15 |
| —OH | 104 | +5.7 (*c*, 2.0 in in ethanol) | $C_{17}H_{22}N_2O_6$ | Calcd. | 58.25 | 6.36 | 8.01 |
| | | | | Found | 58.17 | 6.38 | 8.03 |
| —$NHCH_2CONHCH[CH_2CH(CH_3)_2]$-$COOC_2H_5$ | 130–131 | −11.2 (*c*, 2.1 in ethanol) | $C_{27}H_{40}N_4O_8$ | Calcd. | 59.08 | 7.35 | 10.21 |
| | | | | Found | 59.07 | 7.31 | 10.18 |

(5.1 ml.); yield 664 mg. (83%), m.p. 149–150°, $[\alpha]^{25}D$ +23.1 (*c*, 1.21 in ethanol).

*Anal.* Calcd. for $C_{15}H_{18}N_2O_6$: C, 55.86; H, 5.63; N, 8.69. Found: C, 55.61; H, 5.58; N, 8.54.

**Succinyl(glycine Ethyl Ester, L-Glutamic Acid Diethyl Ester) (XVII).**—This compound was prepared by the procedure for XIII. The final product was recrystallized from ethyl acetate–petroleum ether; yield, 70%, m.p. 96–97°, $[\alpha]^{25}D$ −14.0 (*c*, 1.18 in methanol).

*Anal.* Calcd. for $C_{17}H_{28}N_2O_8$; C, 52.56; H, 7.26; N, 7.21. Found: C, 52.57; H, 7.24; N, 7.26.

**Ethyl β-Carboxypropionyl-DL-phenylalanate (XVIII).**—Succinic anhydride (2.5 g., 0.025 mole) was dissolved in chloroform (100 ml.) and this solution was poured into a solution of ethyl DL-phenylalanate hydrochloride (5.75 g., 0.025 mole) in chloroform (50 ml.) containing tributylamine (3.48 ml). The mixture was stirred for 1 hr. at room temperature, then the reaction mixture was allowed to stand overnight. The solvent was evaporated *in vacuo* at 50–60° and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with *N* hydrochloric acid and water, then the ethyl acetate was evaporated *in vacuo*. The product was crystallized from ethyl acetate–petroleum ether; yield 5.80 g. (80%), m.p. 103–104°.

*Anal.* Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.77. Found: C, 61.29; H, 6.68; N, 4.83.

**Succinyl(DL-phenylalanine Ethyl Ester, L-Glutamic Acid Diethyl Ester) (XIX).**—This compound was prepared by the procedure for XIII; yield, 65%, m.p. 83–84°, $[\alpha]^{25}D$ +8.3 (*c*, 0.7 in ethanol).

*Anal.* Calcd. for $C_{24}H_{34}N_2O_8$: C, 60.23; H, 7.16; N, 5.85. Found: C, 59.94; H, 6.87; N, 5.82.

**Succinyl(DL-phenylalanine Ethyl Ester, ω-Nitro-L-arginine Methyl Ester) (XX).**—Ethyl β-carboxypropionyl-DL-phenylalanate (2.933 g., 0.01 mole) was dissolved in dioxane (50 ml.). After the solution had been cooled to 0°, ethyl chloroformate (0.96 ml.) was added, and the mixture stirred for 15 min. Methyl ω-nitro-L-arginate hydrochloride was dissolved in hot methanol, containing triethylamine (1.40 ml.). The mixture was allowed to stand for 10 min., then the solvent was evaporated *in vacuo*. The residue, methyl ω-nitro-L-arginate was dissolved in dioxane–dimethylformamide (50:50) and this solution was poured into the mixed anhydride of ethyl β-carboxypropionyl-DL-phenylalanate. The mixture was stirred at room temperature for 2 hr. During this time the triethylamine hydrochloride crystallized and was separated by filtration. The solvent was evaporated *in vacuo* and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with *N* hydrochloric acid, water, 5% sodium bicarbonate, and water. The solvent was evaporated *in vacuo* and the product crystallized from methanol–petroleum ether; yield 3.70 g. (73%), m.p. 114–116°, $[\alpha]^{25}D$ −1.8 (*c*, 1.0 in methanol).

*Anal.* Calcd. for $C_{22}H_{32}N_6O_8$: C, 51.96; H, 6.34; N, 16.53. Found: C, 51.84; H, 6.37; N, 16.34.

**Ethyl β-Carboxypropionyl-L-phenylalanate (XXI).**—This compound was prepared by the procedure for XVIII. The final product was crystallized from ethyl acetate–petroleum ether; yield 78%, m.p. 83–84°, $[\alpha]^{25}D$ +17.7 (*c*, 1.0 in methanol).

*Anal.* Calcd. for $C_{15}H_{19}NO_5$: C, 61.42; H, 6.53; N, 4.77. Found: C, 61.39; H, 6.54; N, 4.81.

**Succinyl(L-phenylalanine Ethyl Ester, ω-Nitro-L-arginine Methyl Ester) (XXII).**—This compound was prepared by the procedure for XX. The final product was crystallized from methanol–petroleum ether; yield 70%, m.p. 124–126°, $[\alpha]^{25}D$ −5.0 (*c*, 1.6 in methanol).

*Anal.* Calcd. for $C_{22}H_{32}N_6O_8$: C, 51.96; H, 6.34; N, 16.53. Found: C, 51.96; H, 6.49; N, 16.63.

**Methyl β-Carboxypropionyl-O-benzyl-L-tyrosinate (XXIII).**—This compound was prepared by the procedure for XVIII. Succinic anhydride (1.0 g. 0.01 mole) in chloroform (75 ml.) was combined with methyl O-benzyl-L-tyrosinate hydrochloride (3.21 g., 0.01 mole) in the presence of tributylamine (2.38 ml.). The final product was crystallized from benzene–petroleum ether; yield 3.51 g. (84%), m.p. 85–86°, $[\alpha]^{25}D$ +23.14 (*c*, 1.08 in ethanol).

*Anal.* Calcd. for $C_{21}H_{23}NO_6$: C, 65.44; H, 6.01; N, 3.63. Found: C, 65.31; H, 5.96; N, 3.57.

**Ethyl N-Carbobenzoxyglycyl-L-phenylalanate (XXIV).**—N-Carbobenzoxyglycine[22] (4.18 g., 0.02 mole) was dissolved in chloroform (100 ml.) and triethylamine (2.8 ml., 0.02 mole) was added. The mixture was cooled at −5°, and ethyl chloroformate (1.91 ml., 0.02 mole) was added. The mixture was stirred for 30 min. After this, a solution of L-phenylalanine ethyl ester hydrochloride (3.86 g., 0.02 mole) and triethylamine (2.8 ml., 0.02 mole) in chloroform (25 ml.) was added. The mixture was stirred overnight at room temperature, and the solvent was evaporated under reduced pressure. The residue, a colorless oil, was dissolved in ethyl acetate (200 ml.) and this solution was washed with 1 *N* hydrochloric acid, water, 5% aqueous sodium bicarbonate, and water, and dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo*. Different attempts to crystallize the oil were unsuccessful; yield 6.3 g. (80%).

Note: Kenner and Stedman,[23] who used the method of anhydrides of sulfuric acid, reported the product as an oil.

**N-Carbobenzoxyglycyl-L-phenylalanine (XXV).**—Ethyl N-carbobenzoxyglycyl-L-phenylalanate (3.86 g., 0.01 mole) was dissolved in ethanol (40 ml.) and 1 *N* sodium hydroxide was added during the course of 30 min. The mixture was stirred for 2 hr. at room temperature. Next, 1 *N* hydrochloric acid (12 ml.) was added to the mixture, and the solution was evaporated to dryness under reduced pressure. The residue was dissolved in ethyl acetate, washed with water, and dried over anhydrous sodium sulfate. By careful addition of petroleum ether (b.p. 30–60°), white needles of N-carbobenzoxyglycyl-L-phenylalanine were obtained; yield 2.86 g. (80%), m.p. 126–127° (lit.,[19] m.p. 126–127°).

**Ethyl Glycyl-L-phenylalanate Hydrochloride (XXVI).**—Ethyl N-carbobenzoxyglycyl-L-phenylalanate (6.3 g., 0.015 mole) was dissolved in 95% ethanol (200 ml.) and 4 *N* hydrochloric acid (5 ml.). The product was hydrogenated for 5 hr. at room temperature and at atmospheric pressure over 10% palladium on carbon (2.0 g.). The catalyst was separated by filtration and the solvent evaporated under reduced pressure. The oily product was dissolved in water (200 ml.), and the solution washed with ethyl acetate (50 ml.). Water was removed *in vacuo* at 50–55° over a period of 24 hr. Crystals were obtained by dissolution of the oily residue in absolute ethanol followed by careful addition of anhydrous ether. The hydrochloride was recrystallized from ethanol–ether; yield 3.5 g., m.p. 139–140°, $[\alpha]^{25}D$ +3.2 (*c*, 2.0 in ethanol).

*Anal.* Calcd. for $C_{13}H_{19}N_2O_3Cl$: C, 54.45; H, 6.65; N, 9.76. Found: C, 54.53; H, 6.42; N, 10.09.

**Succinylbis(glycyl-L-phenylalanine Ethyl Ester) (XXVII).**—Ethyl glycyl-L-phenylalanate hydrochloride (3.20 g., 0.0112 mole) was dissolved in dioxane (150 ml.) and triethylamine (1.54 ml., 0.0112 mole) was added. The free amine was cooled in an ice–salt mixture to −5°. Triethylamine (1.54 ml., 0.0112 mole) and a solution of succinyl dichloride (0.867 g., 0.0056 mole) in dioxane (10 ml.) were then added dropwise and simultaneously from the two dropping funnels to the stirred and cooled solution. When the addition was completed, the reaction mixture was stirred for 2 hr. at room temperature. The solvent was evaporated *in vacuo* at 50–60° and the residue dissolved in ethyl acetate. This solution was washed with 1 *N* hydrochloric acid, water, 3% aqueous sodium bicarbonate, and water, and then dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the partially solidified colorless residue was recrystallized from a mixture of ethanol–ether;

(22) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

(23) G. H. Kenner and J. Stedman, *J. Chem. Soc.*, 2069 (1952).

yield 1.7 g. (53%), colorless crystals, m.p. 90°, $[\alpha]^{25}D$ +2.1 (*c*, 2.1 in ethanol).

*Anal.* Calcd. for $C_{30}H_{38}N_4O_8$: C, 61.88; H, 6.58; N, 9.71. Found: C, 61.07; H, 6.66; N, 9.99.

**Succinylbis(glycyl-L-phenylalanine) (XXVIII).**—Succinylbis(glycyl-L-phenylalanine ethyl ester) (1.0 g., 1.72 mmoles) was dissolved in dioxane (15 ml.), and 1 *N* sodium hydroxide (3.80 ml.) was added. The mixture was stirred at 15° for 2 hr. Water (50 ml.) was added to the solution. The solution was extracted once with ethyl acetate (20 ml.) and the aqueous layer was acidified to Congo red with 4 *N* hydrochloric acid. The acidified solution was then extracted with ethyl acetate, (3 × 25 ml.) at 35–40°. The combined extracts were dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo*, and the residue was recrystallized from ethyl acetate; yield 0.65 g. (72%), m.p. 138–140°, $[\alpha]^{25}D$ +28.0 (*c*, 1.0 in *N* NaOH.

*Anal.* Calcd. for $C_{26}H_{30}N_4O_8$: C, 59.35; H, 5.74; N, 10.65. Found: C, 58.98; H, 5.97; N, 10.53.

**Ethyl N-Carbobenzoxyglycyl-L-leucinate (XXIX).**—This compound was prepared from N-carbobenzoxyglycine (4.08 g.) and ethyl L-leucinate hydrochloride[24] (7.8 g.) according to the procedure described by J. R. Vaughan.[25] The product was a colorless oil; yield, 10.5 g. (75%).

**Ethyl Glycyl-L-leucinate Hydrochloride (XXX).**—Ethyl N-carbobenzoxyglycyl-L-leucinate (10.5 g., 0.03 mole) was dissolved in 95% ethanol (200 ml.) and 4 *N* hydrochloric acid (10 ml.). The compound was hydrogenated for 6 hr. at room temperature and atmospheric pressure over 10% palladium on carbon (3.0 g.). Filtration separated the catalyst, and the solvent was evaporated under reduced pressure. The residue was dissolved in water (200 ml.), and the solution washed with ethyl acetate (2 × 50 ml.). Water was removed *in vacuo* at 50°. The oily residue was washed with ethyl acetate and petroleum ether. Ethyl glycyl-L-leucinate hydrochloride was crystallized from ethanol-ether; yield 6.1 g. (80%), m.p. 150–160° (lit.,[26] m.p. 161–162°), $[\alpha]^{25}D$ −35.0 (*c*, 2.0 in ethanol).

**Succinylbis(glycyl-L-leucine Ethyl Ester) (XXXI).**—In a 300-ml., three-neck, round-bottom flask fitted with a motor-driven stirrer and two dropping funnels, ethyl glycyl-L-leucinate hydrochloride (3.03 g., 0.012 mole) was dissolved in a mixture of dioxane (50 ml.), and chloroform (50 ml.), then triethylamine (1.66 ml., 0.012 mole) was added. The mixture was cooled in ice water to 5–10°. Triethylamine (1.66 ml.) an a solution of succinyl dichloride (0.93 g.) in dioxane (10 ml.) were then added dropwise and simultaneously from the two dropping funnels to the stirred and cooled solution during approximately 1 hr. When the addition was completed the reaction mixture was stirred at room temperature overnight. The insoluble triethylamine hydrochloride separated from the reaction mixture and was filtered out. The solvent was evaporated under reduced pressure, and the residue was dissolved in ethyl acetate (200 ml.). This solution was then washed with 1 *N* hydrochloric acid, water, 3% aqueous bicarbonate, and water and then dried over anhydrous sodium sulfate. The solvent was evaporated *in vacuo* and the oily residue was dissolved in absolute ethanol (5 ml.) and precipitated with ether (60 ml.); yield 1.5 g. (50%), m.p. 114°, $[\alpha]^{25}D$ −34.2 (*c*, 2.0 in ethanol).

*Anal.* Calcd. for $C_{24}H_{42}N_4O_8$: C, 56.12; H, 8.24; N, 10.89. Found: C, 56.18; H, 8.26; N, 10.78.

**Succinylbis(glycine-L-leucine) (XXXII).**—Succinylbis(glycyl-L-leucine ethyl ester) (2.57 g., 0.005 mole) was treated with sodium hydroxide according to the procedure described above for the preparation of XXVIII. The crystalline product, after two recrystallizations from ethyl acetate–ether, melted at 124°; yield 1.72 g. (75%), $[\alpha]^{25}D$ −23.5 (*c*, 0.9 in *N* NaOH).

*Anal.* Calcd. for $C_{20}H_{34}O_8N_4$: C, 52.38; H, 7.47; N, 12.22. Found: C, 53.49; H, 7.40; N, 12.15.

**Ethyl β-Carboxypropionylglycyl-L-phenylalanate (XXXIII).**—Glycyl-L-phenylalanine ethyl ester hydrochloride (1.6 g., 0.0056 mole) was dissolved in chloroform (70 ml.), and triethylamine (0.77 ml.) was added. A solution of succinic anhydride (0.56 g., 0.0056 mole) in chloroform (50 ml.) was subsequently added under anhydrous conditions. The reaction mixture was allowed to stand overnight at room temperature and refluxed for 5 min. at the end of that time. The solvent was evaporated under reduced pressure at 40–50°. The residue was dissolved in ethyl acetate. The solution was washed with 1 *N* hydrochloric acid and water, and then dried over anhydrous sodium sulfate. The solvent was concentrated under reduced pressure at 40–50°, and the product was precipitated with petroleum ether (30–60°). Ethyl β-carboxypropionylglycyl-L-phenylalanate, yield 1.3 g. (66%), was obtained as white crystals, which, after recrystallization from ethyl acetate, melted at 104°, $[\alpha]^{25}D$ +5.7 (*c*, 2.0 in ethanol).

*Anal.* Calcd. for $C_{17}H_{22}N_2O_6$: C, 58.25; H, 6.36; N, 8.01. Found: C, 58.17; H, 6.38; N, 8.03.

**Succinyl(glycyl-L-phenylalanine Ethyl Ester, Glycyl-L-leucine Ethyl Ester) (XXXIV).**—Ethyl β-carboxypropionylglycyl-L-phenylalanate (1.75 g., 0.005 mole) was dissolved in chloroform (50 ml.), and triethylamine (0.69 ml.) was added. The mixture was cooled at −5°, and ethyl chloroformate (0.477 ml., 0.005 mole) was added. The solution was stirred for 1 hr., then a solution of glycyl-L-leucine ethyl ester hydrochloride (1.26 g., 0.005 mole) and triethylamine (0.69 ml.) in chloroform (50 ml.) was slowly added. The mixture was allowed to stand for 12 hr., then washed with 1 *N* hydrochloric acid, water, 3% aqueous bicarbonate, and water. The solution was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The oily residue was dissolved in absolute ethanol and precipitated with anhydrous ether; yield 1.51 g. (55.5%), m.p. 130–131°, $[\alpha]^{25}D$ −11.2 (*c*, 2.1 in ethanol).

*Anal.* Calcd. for $C_{27}H_{40}N_4O_8$; C, 59.08; H, 7.35; N, 10.21. Found: C, 59.07; H, 7.31; N, 10.18.

The products and intermediates prepared are shown in Table I.

(24) F. Röhmann, *Ber.*, **30**, 1978 (1897).

(25) J. R. Vaughan, *J. Am. Chem. Soc.*, **73**, 5553 (1951).

(26) E. Abderhalden and W. Z. Kröner, *Z. physiol. Chem.*, **168**, 201 (1927).