sodium chloride over a period of about 1 hr. The chloroform was removed under reduced pressure leaving a residue of 2-acetoxypropylmercuric chloride which crystallized on standing overnight, m.p. 54.4–55.5°.

The other mercurials listed in Table III were prepared by a similar method.

Kinetic Measurement.—The same method as was described in the previous paper[4] was used without any change.

Organotin Esters of Amino Acids and Their Use In Peptide Syntheses

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Trialkyltin esters of amino and N-acylamino acids were prepared and their chemical properties were investigated. The use of the trialkyltin group as a protective group in the syntheses of peptides is described.

While organotin esters of aliphatic and aromatic carboxylic acids have been synthesized[1-3] and biologically tested, especially as fungicides,[4] those of amino acids have received little attention. The preparation of the tributyl- and triphenyltin esters of N-acetylglycine was reported.[5] A more recent work claims the preparation of the trimethyltin ester of α-alanine and the triethyltin ester of β-alanine.[6]

In the present work the synthesis and chemical properties of organotin esters of both amino and N-acylamino acids were investigated. They were found also to be suitable for use as intermediates in the syntheses of peptides.

By heating equivalent amounts of the amino or N-acylamino acids with trialkyltin hydroxide or oxide in benzene or toluene, the respective organotin esters were obtained (Table I). The water formed in the reaction was removed by azeotropic distillation.

$$2R_3SnOH \text{ or } (R_3Sn)_2O + 2R'CH(NHR'')COOH \longrightarrow 2R'CH(NHR'')COOSnR_3 + 2H_2O \text{ or } H_2O$$

$R = C_2H_5, C_4H_9$
$R'' = H, CH_3CO, C_6H_5CO, C_6H_5CH_2OCO$

In the case of glycine, alanine, tyrosine, and tryptophan the addition of dimethylformamide was necessary for completing the reaction.

The investigated monoacidic amino acids required 1 equiv. of organotin oxide or hydroxide for complete reaction and dissolution, while aspartic acid and tyrosine required 2 equiv.

The tri-*n*-butyltin esters of α-alanine, α-aminobutyric acid, valine, and leucine were isolated by distillation under high vacuum. They had relatively high melting points and were soluble in organic solvents.

The organotin esters of the N-acylamino acids were soluble in alcohol, benzene, or toluene and insoluble in cold petroleum ether. They were stable to water and alcohol. The triethyltin esters had generally higher melting points than the corresponding tributyltin compounds.

Owing to the high electropositivity of the tin atom, the trialkyltin esters were attacked readily by strong electrophilic and nucleophilic reagents as follows.

$$R-C(=O)-OSnR_3 \xrightarrow{OH^-} RCOO^- + R_3SnOH$$

$$R-C(=O)-OSnR_3 \xrightarrow{HX} RCOOH + R_3SnX$$

These reactions are very fast, and we found that they can be used also for the rapid quantitative volumetric determination of organotin esters. Thus organotin esters can be titrated quantitatively with sodium methoxide in benzene–methanol or with perchloric acid in dioxane, and with aqueous sodium hydroxide or hydrochloric acid, using thymol blue as indicator.

Heating the N-acylaminotin esters with benzylamine or ammonia under anhydrous conditions in nonhydroxylic solvents such as toluene did not lead to cleavage of the ester group or to amidation, while in the presence of water or alcohol these esters were readily split to give the ammonium salt of the N-acylamino acids. This inability for amide formation is in contrast to the behavior of ordinary alkyl esters which give amides under such conditions. This behavior prevents the use of the organotin esters as acylating agents, indicating the weak electrophilic character of their carbonyl group. Further evidence for this is obtained from the infrared spectra of the organotin esters, which did not show the characteristic absorption of the carbonyl group of alkyl esters[7] at 1740–1750 cm.$^{-1}$. Strong absorptions were found in the region 1550–1600 cm.$^{-1}$ (COO^-, amide).[8] The spectra also showed absorptions at about 870 (Sn–O) and about 1050–1070 cm.$^{-1}$ (Sn–C).[9]

The organotin esters of the N-acylamino acids were stable to electrophilic reagents such as ethyl chloroformate and 2,4-dinitrofluorobenzene, even on heating in toluene solution. The inertness to the last reagent was especially interesting in view of the extreme insolubility of trialkyltin fluorides.[2]

Acetic acid was found to cleave the organotin esters immediately, giving the trialkyltin acetate besides the free N-acylamino acids.

(1) J. G. A. Luijten and J. G. M. Van der Kerk, "Investigations in the Field of Organotin Chemistry," Tin Research Institute, Greenford, Middlesex, England, 1958, p. 92.

(2) R. K. Ingham, S. D. Rosenberg, and H. Gilman, *Chem. Rev.*, **60**, 459 (1960).

(3) R. A. Cummins and P. Dunn, *Australian J. Chem.*, **17**, 185 (1964).

(4) Ref. 1, p. 54; *Tin Its Uses*, **No. 63**, 13 (1964); **No. 64**, 5 (1964).

(5) N. V. Philips' Gloeilampenfabrieken, Dutch Patent 96,805 (Jan. 16, 1961); *Chem. Abstr.*, **55**, 27756 (1961).

(6) D. A. Kochkin and S. G. Verenikina, *Tr. Nauchn. Issled. Vitamin Inst.*, **8**, 39 (1961).

(7) M. S. C. Flett, "Characteristic Frequencies of Chemical Groups in the Infrared," Elsevier Publishing Co., London, 1963, p. 39.

(8) See ref. 7, pp. 35, 23.

(9) V. S. Griffiths and G. A. W. Dervish, *J. Mol. Spectry.*, **11**, 81 (1963).

TABLE I

TRI-*n*-ALKYLTIN ESTERS OF AMINO ACIDS

Amino acids	Yield, %	M.p., °C.	B.p., °C. (0.07 mm.)	Formula	C, % Calcd.	C, % Found	H, % Calcd.	H, % Found	N, % Calcd.	N, % Found	Mol. wt. Calcd.	Mol. wt. Found
Tri-*n*-butyltin Esters of N-Acylamino Acids												
Carbobenzoxyglycine	93	78		$C_{22}H_{37}NO_4Sn$[a]	53.0	53.0	7.4	7.6	2.8	2.9	498	498[b]
Acetylglycine	96	122		$C_{16}H_{33}NO_3Sn$	47.3	47.2	8.1	7.9	3.4	3.3	406	406,[b] 408[c]
Acetyl-DL-methionine	91	25		$C_{19}H_{39}NO_3SSn$	47.5	47.6	8.1	8.1	2.9	3.1		
Acetyl-DL-valine	Quant.	121		$C_{18}H_{39}NO_3Sn$	50.9	51.0	8.7	8.5	3.1	3.3	448	448,[b] 447,[c] 446[d]
Acetyl-DL-leucine	88	35		$C_{20}H_{41}NO_3Sn$	52.0	52.6	8.9	9.1	3.0	3.3	462	462[d]
Benzoyl-DL-phenylalanine	93	35		$C_{28}H_{41}NO_3Sn$	60.2	60.2	7.3	7.3	2.5	2.6	558	556,[c] 555[e]
Triethyltin Esters of N-Acylamino Acids												
Acetylglycine	89	110		$C_{10}H_{21}NO_3Sn$[f]	37.3	37.6	6.6	6.6	4.3	4.3		
Benzoylglycine	92	60		$C_{15}H_{23}NO_3Sn$	46.9	47.4	6.0	6.1	3.6	3.7		
Carbobenzoxyglycine	82	60		$C_{16}H_{25}NO_4Sn$	46.4	47.0	6.0	6.0			414	416,[c] 414[d]
Acetyl-DL-valine	86	157		$C_{13}H_{27}NO_3Sn$	42.9	43.0	7.4	7.4	3.8	3.8	364	364,[d] 360[e]
Benzoyl-DL-phenylalanine	97	119		$C_{22}H_{29}NO_3Sn$	55.7	55.8	6.1	6.1	3.0	3.2	474	472[d]
Tri-*n*-butyltin Esters of Amino Acids[g]												
DL-α-Alanine[h]	75	130–232	133–136	$C_{15}H_{33}NO_2Sn$[i]	47.6	47.5	8.7	8.7	3.7	3.5	378	379[b]
DL-α-Aminobutyric acid	90	110	138–140	$C_{16}H_{35}NO_2Sn$[j]	49.0	48.8	8.9	8.7	3.6	3.4	392	394[b]
DL-Valine	89	60	143–146	$C_{17}H_{37}NO_2Sn$[k]	50.0	50.1	9.1	9.1	3.4	3.5	406	403[b]
DL-Leucine	72	93–95	148–150	$C_{18}H_{39}NO_2Sn$[l]	51.4	51.4	9.3	9.4	3.3	3.4	420	420[b]

[a] *Anal.* Calcd.: Sn, 23.9. Found: Sn, 24.3. [b] Determined by titration with 0.1 *N* sodium hydroxide. [c] Determined by anhydrous titration with $NaOCH_3$. [d] Determined by anhydrous titration with 0.1 *N* perchloric acid in dioxane. [e] Determined by titration with 0.1 *N* hydrochloric acid. [f] Calcd.: Sn, 37.0. Found: Sn, 37.9. [g] The amino acid was heated with tri-*n*-butyltin oxide in toluene (150 ml.) for about 30 min. and the water was removed azeotropically. The ester crystallized out on distillation under high vacuum. [h] Dimethylformamide (20 ml.) and toluene (150 ml.) were used. [i] *Anal.* Calcd.: Sn, 31.5. Found: Sn, 31.4. [j] *Anal.* Calcd.: Sn, 30.3. Found: Sn, 30.0. [k] *Anal.* Calcd.: Sn, 29.3. Found: Sn, 29.5. [l] *Anal.* Calcd.: Sn, 28.3. Found: Sn, 28.3.

The trialkyltin esters of the amino acids behaved differently from those of simple carboxylic acids or of the N-acylamino acids. On contact with reagents such as water, ethanol, benzyl alcohol, benzoic acid, and *m*-cresol the former decomposed readily and quantitatively to the free amino acids. Under anhydrous conditions they were stable to amines such as benzylamine. They could be acetylated by acetic anhydride in the presence of triethylamine which neutralized the acetic acid formed in the reaction.

It was shown that although amines did not cleave the organotin esters of N-acylamino acids under anhydrous conditions, they did so in the presence of water or alcohol. The high sensitivity of the amino acid organotin esters to water or alcohol may also be due to the presence of their free basic amino group.

In the light of their high sensitivity to water, it appeared that the recently reported synthesis[6] of triethyltin ester of β-alanine by reacting β-alanine with triethyltin hydroxide in water could not have led to the desired compound. We prepared the triethyltin ester of β-alanine by heating the amino acid with triethyltin hydroxide in toluene. It crystallized out from the toluene solution on cooling. It melted at 151–152° while the reported melting point[6] was given as 115–116°. The triethyltin ester of β-alanine behaved like the other organotin esters of free amino acids and decomposed readily in the presence of water.

Use of the Amino Acid Tin Esters in Peptide Syntheses.—It was found feasible to use the trialkyltin group as a reversible masking group for the carboxyl function in the syntheses of peptides, instead of the generally used alkyl esters. The advantages were their easy preparation in almost quantitative yields and their easy removal from the prepared peptides by dilute acid or base. Furthermore the trialkyltin residue could be recovered from the reaction mixture as the trialkyltin acetate.

No racemization occurred in the course of the preparation of tri-*n*-butyltin L-leucinate. On decomposition of the ester with water, the recovered free amino acid showed its characteristic specific rotation.

The peptides were prepared using either the mixed carboxylic carbonic anhydride[10] or the active ester[11] methods. The trialkyltin ester of the amino acid, prepared in toluene or toluene–dimethylformamide solution, was added to the mixed anhydride or the active ester of an N-carbobenzoxyamino acid. The yields were generally good except in the case of glycine or β-alanine.

In the dicyclohexylcarbodiimide method for peptide syntheses, the trialkyltin group cannot be used as a protective group. Although carbodiimide alone, when added to a solution of the organotin esters did not cause decomposition, addition of a carbobenzoxy amino acid to the reaction mixture led, due to its acidity, to cleavage of the organotin ester and precipitation of the free amino acid.

Experimental

Melting points were determined on a Fisher-Johns apparatus. Tri-*n*-butyltin oxide, pure grade, was obtained from Fluka.

(10) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961, pp. 978–982.

(11) See ref. 10, pp. 1027–1048.

Triethyltin hydroxide was prepared according to Van der Kerk, *et al.*[12] The concentrations of the hydroxide and oxide were determined by titration with 0.1 *N* hydrochloric acid in aqueous ethanol solution, using bromothymol blue as indicator (yellow end point). The solvents used were dried by standard methods.

Preparation of Trialkyltin Esters of N-Acylamino Acids.—A typical example is described below, the others being summarized in Table I.

Tri-*n*-butyltin Ester of N-Benzoylglycine.—N-Benzoylglycine (1.79 g., 0.01 mole) was heated with tri-*n*-butyltin oxide (2.56 g., 0.0086 equiv.) in dry benzene (100 ml.). Most of the benzene was distilled to remove azeotropically thew ater formed in the reaction. The remaining solution was filtered to remove unreacted material and evaporated *in vacuo*. The residual oil was washed with cold petroleum ether several times, and the tri-*n*-butyltin ester of N-benzoylglycine (3.6 g., 90%) crystallized out, m.p. 52°.

Anal. Calcd. for $C_{21}H_{35}NO_3Sn$: C, 53.8; H, 7.5; N, 3.0; Sn, 25.4; mol. wt., 468. Found: C, 53.4; H, 7.5; N, 3.2; Sn, 24.8; mol. wt., 469 (titration with 0.1 *N* hydrochloric acid), 468 (with sodium hydroxide), 476 (with sodium methoxide).

Tri-*n*-butyltin Ester of N-Benzoyl-DL-phenylalanine.—This ester was prepared as described above from N-benzoylphenylalanine and tributyltin oxide (Table I). It was also prepared in lower yield by a different method as follows.

The sodium salt of N-benzoyl-DL-phenylalanine (2.91 g., 0.01 mole) was suspended in dry benzene (50 ml.) and heated under reflux with tri-*n*-butyltin chloride (3.25 g., 0.01 equiv.) for 2 hr. The reaction mixture was further stirred at room temperature for 2 days, filtered, and evaporated *in vacuo*. The viscous oil which remained was washed several times with petroleum ether. The tri-*n*-butyltin ester of N-benzoyl-DL-phenylalanine crystallized out on standing at −20° for 2 days; yield 3 g. (53%), m.p. 35°.

Anal. Calcd. for $C_{28}H_{41}NO_3Sn$: C, 60.2; H, 7.3; N, 2.5. Found: C, 60.2; H, 7.3; N, 2.6.

Trialkyltin Esters of Amino Acids.—Two examples are described below; the others are summarized in Table I.

Di(tri-*n*-butyltin Ester) of DL-Aspartic Acid.—DL-Aspartic acid (2.66 g., 0.02 mole) and tri-*n*-butyltin oxide (12 ml., 0.04 equiv.) were heated in toluene (150 ml.). The solution was distilled slowly, concentrated to a volume of 50 ml., filtered, and evaporated *in vacuo*. The oily residue was washed several times with petroleum ether, and the ester of DL-aspartic acid crystallized out; yield 8.5 g. (60%), m.p. 80–82°.

Anal. Calcd. for $C_{28}H_{59}NO_4Sn_2$: C, 47.3; H, 8.3; N, 2.0. Found: C, 47.3; H, 8.3; N, 2.2.

Triethyltin Ester of β-Alanine.—Triethyltin hydroxide (2.5 g., 0.011 mole) was heated with β-alanine (1 g., 0.011 mole) in dry toluene (150 ml.). The toluene was slowly distilled off to remove azeotropically the water formed and the solution was concentrated to a small volume and cooled. The triethyltin ester of β-alanine (3.3 g., quantitative yield) crystallized out, m.p. 151–152°. It decomposed readily in the presence of water to yield β-alanine.

Anal. Calcd. for $C_9H_{21}NO_2Sn$: N, 4.8; mol. wt., 294. Found: N, 4.9; mol. wt., 300 (by titration with 0.1 *N* sodium hydroxide).

Reactions of the Organotin Esters of N-Acylamino Acids. A. Reaction with Aqueous Benzylamine.—To a solution of tri-*n*-butyltin ester of N-acetylglycine (2 g., 0.005 mole) in dioxane (20 ml.) was added a solution of benzylamine (1.07 g., 0.01 mole) in dioxane (10 ml.) and water (5 ml.). The reaction mixture was stirred at room temperature for 4 hr. and evaporated *in vacuo*. The residual oil was washed several times with petroleum ether and the benzylamine salt of N-acetylglycine crystallized out; yield 1.1 g. (quantitative), m.p. 137°. It was identified by mixture melting point and by comparison of its infrared spectrum with that of an authentic sample prepared by heating equimolar amounts of N-acetylglycine and benzylamine in dry dioxane.

Anal. Calcd. for $C_{11}H_{16}N_2O_3$: C, 58.9; H, 7.1; N, 12.5. Found: C, 58.9; H, 7.3; N, 12.5.

B. Reaction with Alcoholic Benzylamine.—Benzylamine (0.2 ml.) was added to a solution of tri-*n*-butyltin ester of N-acetylglycine (0.454 g., 1.12 mmoles) in absolute ethanol (10 ml.) and left overnight. The solution was diluted with a large volume of dry petroleum ether. The benzylamine salt of N-acetylglycine crystallized out; yield 0.12 g. (60%), m.p. 137°.

C. Reaction with Acetic Acid.—The tri-*n*-butyltin ester of N-acetylglycine (2 g., 0.005 mole) was dissolved in ethanol (25 ml.), glacial acetic acid (0.6 ml., 0.01 mole) was added, and the reaction mixture was left for 30 min. at room temperature. The solution was evaporated *in vacuo* and the residue was extracted several times with boiling water to remove the N-acetylglycine which was recovered (450 mg., 77%) on evaporation of the aqueous extracts. The residue from the water extraction was dissolved in alcohol and diluted with water; tri-*n*-butyltin acetate (1.13 g., 91%) precipitated out and was identified by melting point and mixture melting point.

Reaction of Organotin Esters of Amino Acids. A. Reaction with Water.—To the tri-*n*-butyltin ester of L-leucine prepared in toluene (150 ml.) from L-leucine (6 g.), water (1.5 ml.) was added with stirring. The reaction mixture was stirred for 1 hr., and the L-leucine (6 g., quantitative yield) separated out and was filtered, washed with acetone and ether, and dried at 110°. It was identified by paper chromatography. Its specific rotation was $[\alpha]_D$ +15.5° (*c* 4, 6 *N* HCl). The L-leucine used for the above preparation had the same specific rotation, $[\alpha]_D$ + 15.5°, under the same conditions.

The same results were obtained with the tri-*n*-butyltin esters of DL-methionine, β-alanine, and DL-α-aminobutyric acid.

B. Reaction with Alcohols.—To the tri-*n*-butyltin ester of DL-methionine previously prepared from DL-methionine (2.98 g., 0.02 mole) and dissolved in toluene (40 ml.), freshly distilled benzyl alcohol (2.1 ml., 0.02 mole) was added with stirring. A heavy precipitate formed immediately and the reaction mixture was left overnight. The methionine (2.77 g. 93%) was filtered and identified by thin layer chromatography and infrared spectrum.

The same results were obtained with ethanol and other tri-*n*-butyltin esters.

C. Reactions with Amines.—To the tri-*n*-butyltin ester of DL-α-aminobutyric acid (487 mg., 1.25 mmoles) in toluene (3 ml.), benzylamine (0.2 ml., 0.002 mole) was added under anhydrous conditions and the solution was stirred for 12 hr. No reaction occurred as the solution remained clear and no precipitate of free amino acid was observed.

To a solution of tri-*n*-butyltin ester of DL-methionine in toluene (40 ml.), an excess of dry, redistilled aniline was added and the whole was allowed to stand at room temperature for 3 days. No reaction was observed.

D. Reaction of Organotin Esters of Amino Acids with Acetic Anhydride.—To a solution of the tri-*n*-butyltin ester of DL-valine, prepared as described from DL-valine (1.17 g., 0.01 mole), triethylamine (1.4 ml.) was added, followed by acetic anhydride (1 g., 0.01 mole), and the reaction mixture was left at room temperature for 2 hr. The reaction mixture was then heated under reflux for 2 hr., washed with water, and evaporated *in vacuo*. The residual oil was washed several times with petroleum ether, and the tri-*n*-butyltin ester of N-acetyl-DL-valine crystallized out (4.3 g., 93%). It was identified by melting point and mixture melting point with an authentic sample of the ester.

E. Reaction with Benzoic Acid.—To a solution of the tri-*n*-butyltin ester of DL-α-aminobutyric acid (415 mg., 1.06 mmoles) in toluene (3 ml.), a chloroform solution (1 *N*) of benzoic acid (1.5 ml.) was added with stirring. A heavy precipitate of DL-α-aminobutyric acid (102 mg., 93%) separated out immediately and was identified by paper chromatography.

F. Reaction with Cresol.—To a solution of the tri-*n*-butyltin ester of DL-α-aminobutyric acid (409 mg., 1.04 mmoles) in toluene (3 ml.), *m*-cresol (5 drops, excess) was added with stirring. A heavy precipitate of DL-α-aminobutyric acid (90 mg., 84%) separated out immediately.

Synthesis of Peptides Using Organotin Esters of Amino Acids as Intermediates. N-Carbobenzoxyglycyl-DL-phenylalanine.—DL-Phenylalanine (3.28 g., 0.02 mole) was heated in toluene (150 ml.) with tri-*n*-butyltin oxide (11.9 g., 0.04 equiv.) and the water was removed azeotropically with most of the toluene (about 100 ml.). The clear toluene solution of the ester was cooled to 0° and was added with exclusion of moisture to a cold toluene solution of a mixed anhydride prepared from carbobenzoxyglycine (4.18 g., 0.02 mole) and ethyl chloroformate according to Vaughan and Osato.[13] The mixture was stirred for 30

(12) See ref. 1, p. 98.

(13) J. R. Vaughan, Jr., and R. L. Osato, *J. Am. Chem. Soc.*, **74**, 676 (1952).

min. at −5° and at room temperature for 3 hr. Water (35 ml.) was added, and the reaction mixture was stirred for 10 min., followed by the addition of 1 *N* sodium hydroxide solution (50 ml.). After stirring for another 10 min., the aqueous layer was separated and the organic layer was extracted three times with 1 *N* sodium hydroxide solution (30 ml.). The combined alkaline extracts were washed with ether and acidified with hydrochloric acid. N-Carbobenzoxyglycyl-DL-phenylalanine (5.8 g., 81%) precipitated out, m.p. 158°. On recrystallization from aqueous ethanol, the melting point rose to 161° (lit.[13] m.p. 160–162°).

Anal. Calcd. for $C_{19}H_{20}N_2O_5$: C, 64.0; H, 5.6. Found: C, 63.7; H, 5.5.

The tri-*n*-butyltin residue was recovered as the tri-*n*-butyltin acetate as follows. The organic layer which remained after the extraction with alkali was evaporated *in vacuo*. Glacial acetic acid was added to the remaining oil; the solution was left for some minutes and then diluted with water. Tri-*n*-butyltin acetate (13.5 g., 97%) precipitated out and was identified by mixture melting point with an authentic sample.

Using equimolar quantities of phenylalanine and of organotin oxide in the esterification gave similar yields.

N-Carbobenzoxyglycyl-DL-α-alanine. A.—Tri-*n*-butyltin ester of DL-α-alanine prepared as described from 0.02 mole of amino acid was added in the cold with stirring to a mixed anhydride solution prepared from N-carbobenzoxyglycine (0.02 mole) and ethyl chloroformate[13] and left for 5 days at room temperature. The reaction mixture was worked up in the usual manner giving N-carbobenzoxyglycyl-DL-α-alanine (3.5 g., 63%), m.p. 176° (lit.[14] m.p. 176°).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.5; H, 5.8; N, 10.3.

The organotin was recovered from the organic layer as the tri-*n*-butyltin acetate in 93% yield.

B.—The tri-*n*-butyltin ester of DL-α-alanine prepared from α-alanine (0.89 g., 0.01 mole) was added to a mixed anhydride prepared from N-carbobenzoxyglycine (2.09 g., 0.01 mole), triethylamine, and isobutyl chloroformate (1.04 ml., 0.01 mole) by the usual method. The reaction mixture was stirred in the cold (−2°) for 30 min. and at room temperature for 8 hr. more. The precipitate of triethylamine hydrochloride was filtered and the clear solution was titrated with 1 *N* sodium methoxide, using thymol blue as indicator. The blue solution was poured into a large volume of petroleum ether and cooled overnight at −20°. The oil which separated out was dissolved in a small volume of water and acidified with concentrated hydrochloric acid. Crystalline N-carbobenzoxyglycyl-DL-α-alanine precipitated out; yield 1.9 g. (68%), m.p. and m.m.p. 176°.

N-Carbobenzoxyglycyl-DL-methionine.—A toluene solution of tri-*n*-butyltin ester of DL-methionine prepared from DL-methionine (2.98 g., 0.02 mole) was added at −5° to a solution of a mixed anhydride prepared from N-carbobenzoxyglycine (4.18 g., 0.02 mole) and ethyl chloroformate in the usual manner. The reaction mixture was stirred for 1 hr. at 0 to −5° and then for 10 min. at room temperature. Water (50 ml.) was added and the reaction mixture was stirred and left overnight. The organic layer was extracted with 1 *N* sodium hydroxide solution and worked up as before to give N-carbobenzoxyglycyl-DL-methionine, 5.5 g. (81%), m.p. 123° (lit.[15] m.p. 124°) on recrystallization from water.

Anal. Calcd. for $C_{15}H_{20}N_2O_5S$: C, 52.9; H, 5.9; N, 8.2. Found: C, 53.3; H, 5.8; N, 7.9.

N-Carbobenzoxyglycyl-DL-α-amino-*n*-butyric Acid. A.—A cold solution of the tri-*n*-butyltin ester of DL-α-amino-*n*-butyric acid, prepared from the amino acid (0.01 mole), in dry toluene (50 ml.) was added to a cold solution of a mixed anhydride prepared from N-carbobenzoxyglycine (0.01 mole) and isobutyl chloroformate. The reaction mixture was stirred for 30 min. at −2°, left overnight at room temperature, and worked up in the usual manner to yield N-carbobenzoxyglycyl-DL-α-amino-*n*-butyric acid, 2.5 g. (85%), m.p. 158° (lit.[15] m.p. 158°) on recrystallization from water.

B.—A toluene solution of the tri-*n*-butyltin ester of DL-α-aminobutyric acid, prepared from 0.01 mole of the amino acid, was added to a solution of N-carbobenzoxyglycine *p*-nitrophenyl ester (3.3 g., 0.01 mole) and triethylamine (0.01 mole) in dimethylformamide (10 ml.). The reaction mixture was left at room temperature for 24 hr. and then extracted six times with water (25 ml.). The combined aqueous extracts were acidified, and the N-carbobenzoxyglycyl-DL-α-aminobutyric acid (2.4 g., 82%) precipitated out; m.p. 155°, which rose to 158° on recrystallization from water (lit.[15] m.p. 158°).

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.1; H, 6.1. Found: C, 57.1; H, 6.1.

N-Carbobenzoxyglycyl-DL-tryptophan.—DL-Tryptophan (2.04 g., 0.01 mole) was heated in toluene (150 ml.) and dimethylformamide (20 ml.) with tri-*n*-butyltin oxide (2.98 g., 0.01 equiv.) and distilled to a small volume (50 ml.). To the clear solution of the ester, N-carbobenzoxyglycine *p*-nitrophenyl ester (3.3 g., 0.01 mole) in dimethylformamide (10 ml.) was added followed by triethylamine (1.4 ml.) and the reaction mixture was left for 24 hr. at room temperature. The reaction mixture was diluted with ethyl acetate (150 ml.) and washed several times with water. The organic layer was extracted three times with 1 *N* sodium hydroxide (50 ml.). The combined alkaline extracts were washed with ether and acidified. The yellow oil which separated out was taken up in ethyl acetate, washed with water, and evaporated *in vacuo* at 40°. The residue was dissolved in ethyl acetate (15 ml.), petroleum ether (150 ml.) was added, and the solution was left overnight at −20°. N-Carbobenzoxyglycyl-DL-tryptophan precipitated out; 2.5 g. (63.4%), m.p. 180°.

Anal. Calcd. for $C_{21}H_{21}N_3O_5$: C, 63.7; H, 5.3; N, 10.6. Found: C, 63.4; H, 5.5; N, 10.2.

N-Carbobenzoxyglycyl-β-alanine.—A cold solution of the tri-*n*-butyltin ester of β-alanine, prepared from the amino acid (0.01 mole), in toluene–dimethylformamide was added to a mixed anhydride prepared from N-carbobenzoxyglycine (0.01 mole) and isobutyl chloroformate cooled to −5°. The reaction mixture was stirred for 30 min. at −5°, left overnight, and worked up in the usual manner to yield N-carbobenzoxyglycyl-β-alanine (1.1 g., 40%) which melted at 140° (lit.[16] m.p. 140°).

Anal. Calcd. for $C_{13}H_{16}N_2O_5$: C, 55.7; H, 5.7; N, 10.0. Found: C, 55.7; H, 5.5; N, 9.9.

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