overnight at 100° under oil pump vacuum it lost 0.97% water and melted at 240–241° with a sinter at 201°.

Anal. Calcd. for $C_{16}H_{24}NI$: C, 53.78; H, 6.77. Found: C, 53.92; H, 6.59.

1,3-Dimethyl-1-(2-dimethylaminoethyl)-1,2-dihydronaphthalene Hydrobromide.—The methiodide of the β-benzomorphan, 1.8 g., was converted to the methohydroxide with thallous hydroxide. After filtering the thallous iodide the aqueous solution was taken to an oil under reduced pressure and the base then heated in a bath at 170° (0.5 mm.) with distillation of a colorless oil at about 120° (0.5 mm.). In ether solution with hydrogen bromide it gave a crystalline salt, wt., 1.4 g. (88% over-all), m.p. 170–174° (gas). Recrystallized from acetone, it melted at 175–177°.

Anal. Calcd. for $C_{16}H_{24}NBr$: C, 61.93; H, 7.80. Found: C, 62.12; H, 8.12. An ethanol solution showed λ_{max} 265 mμ (ε 9000).

1,3-Dimethyl-1-(2-dimethylaminoethyl)-1,2,3,4-tetrahydronaphthalene hydrobromide was obtained by reduction of the above salt in alcohol with Adams catalyst. It was recrystallized by adding ethyl acetate to a solution in alcohol–acetone, m.p. 202–205°.

Anal. Calcd. for $C_{16}H_{26}NBr$: C, 61.53; H, 8.39. Found: C, 61.81; H, 8.47.

1,2-Dimethylnaphthalene was recovered as the picrate in 18% yield as one of the products resulting from the 280° palladium–charcoal decomposition of the tetrahydronaphthalene base from the preceding hydrobromide.[9] Identification was by a mixture melting point with a known sample.

Acknowledgment.—Nuclear magnetic resonance data were helpfully interpreted by Drs. E. D. Becker and L. A. Cohen and recorded by Mr. R. B. Bradley; configuration assignments of the benzomorphans were generously made by Dr. E. L. May.

The Synthesis of Tryptophan Peptides

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Received December 26, 1962

The preparation of blocked and free dipeptides containing tryptophan and the synthesis of tryptophan benzyl ester are described.

In connection with our work on the specific cleavage of proteins at the tryptophyl residue, we found it necessary to prepare various peptides containing tryptophan as model compounds.

The only studies so far reported in the synthesis of tryptophan peptides are the early work of Abderhalden[1] and the work of Smith[2] on the synthesis of protected tryptophyl peptides through carbobenzoxy tryptophyl chloride, and the preparation of tryptophylglycine[3] and arginyltryptophan[4,5a] as intermediates in the partial synthesis of α and β MSH.[5b]

All the protected tryptophan peptides listed in Table I and the corresponding free peptides listed in Table II previously have not been reported in the literature. They were synthesized by coupling carbobenzoxy-L-tryptophan with the appropriate amino acid benzyl ester by the dicyclohexylcarbodiimide (DCC) method.[6]

The blocked dipeptides containing C-terminal tryptophan were prepared similarly from the appropriate carbobenzoxy-L-amino acid and L-tryptophan benzyl ester, except for carbobenzoxy-L-prolyl-L-tryptophan which was synthesized from carbobenzoxypropyl chloride[7] and free L-tryptophan.

Tryptophan benzyl ester hydrochloride has not been synthesized previously probably owing to the instability of tryptophan at the acid pH values and high temperature needed for esterification. However, we succeeded in synthesizing this compound in 80% yield in one step by a modification of Erlanger's method.[8] The method was to pass phosgene through a suspension of tryptophan in dioxane until the tryptophan was completely dissolved, being converted to the N-carboxy-anhydride.[9] About half the dioxane was distilled so as to remove the excess of phosgene. Benzyl alcohol–ether was added and two to three moles of gaseous hydrogen chloride per mole residue of tryptophan were passed through at 0°. After standing overnight, the ester precipitated. All of the benzyl esters used in this study were synthesized by this method.

The unblocked peptides listed were obtained by catalytic hydrogenation of the blocked peptides in the presence of palladium on charcoal.

The free peptides were chromatographically pure (butanol–acetic acid–water, 25:6:25). On basic hydrolysis all gave tryptophan and the appropriate amino acid in a 1:1 ratio.

Experimental

All melting points are uncorrected. Prior to analysis the free peptides were dried at 80° *in vacuo*, over phosphorus pentoxide. Other compounds were dried *in vacuo* over phosphorus pentoxide at room temperature.

L-Tryptophan Benzyl Ester Hydrochloride.—Dry phosgene was passed at room temperature through a suspension of L-tryptophan (20.4 g.) in anhydrous dioxane (330 ml.) until a clear solution was obtained (about 45 min.). Phosgene was removed by a stream of dry nitrogen and half of the solvent was distilled *in vacuo* at 45°.

Benzyl alcohol (50 ml.) and dry ether (250 ml.), previously saturated with 2–3 moles of gaseous hydrogen chloride per mole residue of tryptophan at 0°, were added, and the solution was left overnight at room temperature. The ester which separated was filtered off and washed with ether. The product was recrystallized from hot water; yield, 80%; m.p. 222°, $[\alpha]^{26}D$ +4° (*c* 2, methanol).

Anal. Calcd. for $C_{18}H_{18}N_2O_2 \cdot HCl$: C, 65.45; H, 5.78; N, 8.48. Found: C, 65.55; H, 5.83; N, 8.28.

Carbobenzoxy-L-tryptophan *p*-Nitrophenyl Ester.—Cbz-L-tryptophan (34 g.) was dissolved in ethyl acetate and *p*-nitrophenol (14 g.) was added. The solution was cooled to 0° and dicyclohexylcarbodiimide (20.5 g.) was added. After 2 hr. at room tem-

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TABLE I

BLOCKED DIPEPTIDES OF L-TRYPTOPHAN

Dipeptide[g]	Yield, %	M.p., °C.	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	$[\alpha]^{25}D$[a]
Z-L-Ala-L-try OBZ	78	105[b]	$C_{29}H_{29}N_3O_5$	69.72	5.85	8.41	69.52	6.00	8.60	−22
Z-L-Leu-L-try OBZ	80	110[b]	$C_{32}H_{35}N_3O_5$	70.92	6.51	7.76	70.81	6.40	7.82	−27
Z-L-Phe-L-try OBZ	70	135[b]	$C_{35}H_{33}N_3O_5$	73.02	5.78	7.30	72.80	5.79	7.10	− 4
Z-L-Pro-L-try	70	183[c]	$C_{24}H_{25}N_3O_5$	66.20	5.74	9.65	66.35	5.78	9.80	−20
Z-L-Try-L-try OBZ	90	75[d]	$C_{32}H_{34}N_4O_5$	72.30	5.50	9.09	72.10	5.65	8.87	− 9
Z-L-Val-L-try OBZ	85	129[d]	$C_{31}H_{33}N_3O_5$	70.58	6.26	7.96	70.65	6.38	8.08	−24
Z-L-Try-L-ala OBZ	80	153[e]	$C_{29}H_{29}N_3O_5$	69.72	5.85	8.41	69.77	5.97	8.38	−22
Z-L-Try-L-leu OBZ	83	114[d]	$C_{32}H_{35}N_3O_5$	70.92	6.51	7.76	71.20	6.53	8.00	−34
Z-L-Try-L-phe OBZ	89	130[f]	$C_{35}H_{33}N_3O_5$	73.02	5.78	7.30	72.90	5.90	7.58	−22
Z-L-Try-L-try OMe	70	196[e]	$C_{31}H_{30}N_4O_5$	69.13	5.50	10.50	69.15	5.48	10.30	−13
Z-L-Try-L-tyr OBZ	85	110[d]	$C_{35}H_{33}N_3O_6$	71.05	5.62	7.10	70.97	5.80	7.02	−23
Z_2-L-Tyr-L-try OMe	78	176[f]	$C_{37}H_{35}N_3O_8$	68.40	5.40	6.50	68.35	5.71	6.60	− 8

[a] *c* 1, methyl alcohol. Recryst. solvent: [b] Ethyl acetate–ether. [c] Ethanol. [d] Ethyl acetate–petroleum ether. [e] Ethyl acetate. [f] Methanol. [g] Abbreviations: Z = C_7H_7OCO, BZ = $C_6H_5CH_2$.

TABLE II

FREE DIPEPTIDES OF L-TRYPTOPHAN

Peptide	Yield, %	$[\alpha]^{25}D$	Formula	Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N	Recrystallization solvent
L-Ala-L-try	85	+19[a]	$C_{14}H_{12}N_3O_3$	61.08	6.22	15.26	61.20	6.30	15.38	Ethyl alcohol–ethyl acetate
L-phe-L-try	78	+ 6[b]	$C_{20}H_{21}N_3O_3H_2O$	65.04	6.23	11.38	65.20	6.35	11.53	Methyl alcohol–ethyl alcohol
L-pro-L-try	85	−35[d]	$C_{16}H_{19}N_3O_3H_2O$	60.18	6.58	13.16	59.88	6.60	13.40	Water–ethyl alcohol
L-Try-L-try	80	−12[c]	$C_{22}H_{22}N_4O_3$	67.67	5.68	14.35	67.56	5.80	14.62	Ethyl alcohol–ethyl acetate
L-Try-L-ala	95	+28[a]	$C_{14}H_{12}N_3O_3$	61.08	6.22	15.26	60.92	6.45	15.05	Water–ethyl alcohol
L-Try-L-leu	93	+18[a]	$C_{12}H_{23}N_3O_3$	64.33	7.30	13.24	64.50	7.50	13.48	Water–ethyl alcohol
L-Try-L-phe	85	+30[b]	$C_{20}H_{21}N_3O_3H_2O$	65.04	6.23	11.38	65.30	6.40	11.54	Methyl alcohol–ethyl alcohol
L-Try-L-tyr	88	+ 8[c]	$C_{20}H_{21}N_3O_4$	65.38	5.76	11.44	65.23	5.67	11.22	Ethyl alcohol–ethyl acetate

[a] *c* 1, water. [b] *c* 1, methyl alcohol. [c] *c* 1, ethyl alcohol. [d] *c* 1, 6 *N* HCl.

perature, the dicyclohexylurea was filtered off and washed with ethyl acetate. The filtrate was evaporated to dryness and the crystalline residue was recrystallized from hot ethanol; yield, 85%; m.p. 105°, $[\alpha]^{25}D$ −4.5° (*c* 5, dimethylformamide).

Anal. Calcd. for $C_{25}H_{24}N_3O_6$: C, 65.35; H, 4.57; N, 9.15; neut. equiv., 459. Found: C, 65.19; H, 4.22; N, 9.03; neut. equiv., 457.

The neutral equivalence value was determined by titration in ethanol with 0.1 *M* sodium methoxide using thymol blue as indicator.[10]

Carbobenzoxy-L-tryptophyl-L-alanine Benzyl Ester.—To a solution of L-alanine benzyl ester hydrochloride (21.5 g., 0.1 mole) in 150 ml. of dichloromethane was added triethylamine (14.4 ml.) and the solution was mixed with another solution of carbobenzoxy-L-tryptophan (33.8 g., 0.1 mole) in 150 ml. of dichloromethane at 0°. Then 20.5 g. of dicyclohexylcarbodiimide was added, and the solution was stirred overnight at room temperature. Dicyclohexylurea was removed by filtration, and the filtrate was washed with 0.5 *N* hydrochloric acid, water, 5% sodium bicarbonate solution, and finally dried over sodium sulfate. The solvent was evaporated *in vacuo*. Upon adding ether, the residue crystallized, and was recrystallized from ethyl acetate; yield, 80%; m.p. 153°, $[\alpha]^{25}D$ −27° (*c* 1, methanol).

Anal. Calcd. for $C_{29}H_{29}N_3O_5$: C, 69.72; H, 5.85; N, 8.41. Found: C, 69.77; H, 5.97; N, 8.38.

The other protected tryptophyl dipeptides were made similarly (Table I).

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Carbobenzoxy-L-phenylalanyl-L-tryptophan Benzyl Ester.—This compound was prepared from carbobenzoxy-L-phenylalanine and L-tryptophan benzyl ester hydrochloride in the manner described earlier. The filtrate was washed with water, 0.5 *N hot* hydrochloric acid, *hot* water, 5% sodium bicarbonate solution, water, and dried over sodium sulfate. The solvent was evaporated *in vacuo*. Upon adding petroleum ether, the oily residue crystallized and was recrystallized from ethyl acetate–ether; yield, 70%; m.p. 135°, $[\alpha]^{25}D$ −4° (*c* 5, methanol).

Anal. Calcd. for $C_{35}H_{33}N_3O_5$: C, 73.02; H, 5.78; N, 7.30. Found: C, 72.80; H, 5.99; N, 7.10.

The remaining tryptophan dipeptides were prepared similarly. Yields and analytical data are given in Table I.

L-Tryptophyl-L-alanine.—A solution of carbobenzoxy-L-tryptophyl-L-alanine benzyl ester (5 g.) in 80% methanol–water was hydrogenated in the presence of 0.5 g. of 10% palladium on charcoal for 4 hr. The catalyst was removed by filtration. The filtrate was evaporated *in vacuo* and, upon adding ethanol, the peptide crystallized, and was recrystallized from water–ethanol; yield, 95%, $[\alpha]^{25}D$ +28° (*c* 1, water).

Anal. Calcd. for $C_{14}H_{12}N_3O_3$: C, 61.08; N, 6.22; N, 15.26. Found: C, 60.92; H, 6.45; N, 15.05.

All of the N and C terminal tryptophan peptides are soluble in methanol. The remaining free peptides were made similarly. Yields and analytical data are given in Table II.

Acknowledgment.—This investigation was supported by research grant no. A-5098 from the National Institutes of Health, U. S. Public Health Service.