[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

POLY-2-AMINO-4-PENTENOIC ACID AND POLYTRYPTOPHAN

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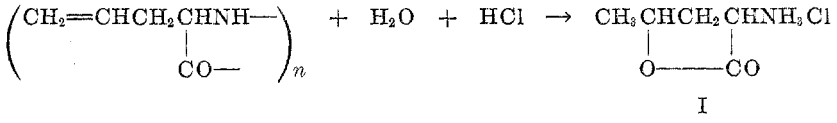
In recent articles (1) methods for synthesizing polypeptides from malonic esters by way of hydroxamic derivatives have been developed. The synthesis is now extended to include polypeptides related to 2-amino-4-pentenoic acid and tryptophan. Infrared spectra have been reported (2) for these two polypeptides.

Since no acidic reagents were used in these syntheses any possible destructive action of acids on tryptophan was avoided. Yields were high in both syntheses, as witnessed by the 51 % conversion of sodium ethyl allylmalonate in four steps into poly-2-amino-4-pentenoic acid. To make this polypeptide by the alternative Leuchs method (3, 4) would involve much lower yields.

The ultraviolet spectra [wavelength in mμ, log extinction coefficient (log ϵ_m)] of alcoholic solutions of tryptophan (275, 3.73; 280, 3.76; 290.5, 3.69) and acetyltryptophan (274, 3.71; 282.5, 3.75; 290.5, 3.69) have been reported by Edwards (5). In the present work it was found that an alcoholic solution of polytryptophan (Fig. 1) gave these values of absorption maxima (mμ, log ϵ_m): 275, 3.71; 282, 3.74; 290.5, 3.67, which are very close to those reported for acetyltryptophan.

When proteins containing tryptophan are hydrolyzed with acids destruction of the tryptophan occurs. Similarly, our polytryptophan yielded only a brown gum on acid hydrolysis.

It was expected that poly-2-amino-4-pentenoic acid also would fail to yield the simple amino acid on acid hydrolysis in view of the known ease of lactonization (4, 6, 7) of the latter by mineral acids. That the polypeptide did contain ethylenic unsaturation before hydrolysis was evident since a solution of it in formic acid decolorized bromine in acetic acid. When this polypeptide was hydrolyzed at 130–140° with hydrochloric acid the major product was the hydrochloride of 2-amino-4-valerolactone, m.p. 192–193°:

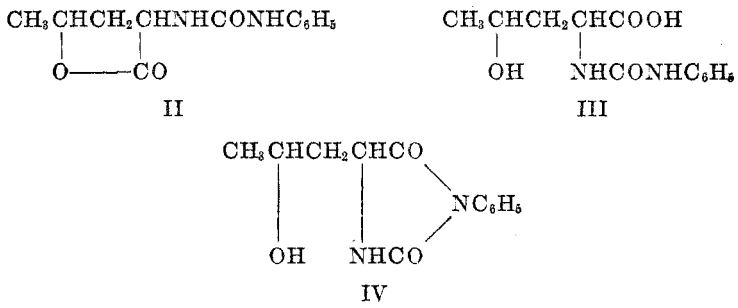


I

In their study of 2-amino-4-hydroxyvaleric acid, Fischer and Leuchs (8) obtained this lactone salt (m.p. 194–196°). They also treated the sodium salt of this acid in aqueous solution with phenyl isocyanate and obtained (on acidification) a phenylureido derivative of m.p. 163–164° which they assigned the lactone structure II because it was easily soluble in alkali. That this same derivative (4) could also be prepared from I was demonstrated by Goering, Cristol, and Dittmer (4), who also prepared a benzoyl derivative (4, 7) of m.p. 140–141°.

As stated above, a lactone salt of m.p. 192–193° was isolated in the present work. From it, a benzoyl derivative of m.p. 140–141° was obtained as expected,

but the phenylureido derivative melted at 152° instead of 164°. Analysis of the 152°-material was correct for $C_{12}H_{16}N_2O_4$, suggesting 2-phenylureido-4-hydroxyvaleric acid (III) and not its lactone (II).



No satisfactory reason suggests itself for the difference of our phenylureido derivative from that of earlier workers, especially in view of the fact that preparations of the latter were made both from the hydroxy acid and its lactone. Our material dissolves readily in sodium hydroxide solution as would be expected for a structure containing a free carboxyl group, but Fischer's derivative also was readily soluble in alkali. Alkali solubility would also be predicted for hydantoin IV, another reasonable structure to consider for $C_{12}H_{14}N_2O_3$.

An infrared spectrum (Fig. 2) of a Nujol mull of the 152°-phenylureido derivative was obtained through the kindness of Dr. K. N. Campbell of the University of Notre Dame. Bands at 2.92 and 5.81 μ pointed to the presence, respectively, of hydroxyl and carboxyl; and the absence of a band at 5.5–5.6 μ indicates absence of a γ-lactone. In contrast, the infrared spectrum of the benzoyl derivative (m.p. 140°), which has an unquestioned lactone structure, showed an intense band at 5.60 μ (Figure 3). The spectra in Fig. 3 were taken in a 0.1-mm. cell with a Beckman self-recording spectrophotometer, model IR2T.

Another feature encountered during the hydrolysis of poly-2-amino-4-pentenoic acid was the isolation of a smaller quantity of a more-soluble lactone salt, m.p. 153°, isomeric with the one melting at 192–193°. These two substances are regarded as the two racemic forms of 2-amino-4-valerolactone hydrochloride. That the 153°-material is not DL-proline hydrochloride (m.p. 156°) was established since the former depressed the m.p. of the latter (9) in a mixture of the two. In keeping with the γ-lactone structure the compound gave a benzoyl derivative (m.p. 127–128°) whose infrared spectrum showed an intense band at 5.60 μ (Fig. 3). The quite different spectrum of isomeric 2-benzamido-4-pentenoic acid is also included.

The following evidence also effectively rules out 2-amino-5-valerolactone hydrochloride as a possible structure to consider. Sorensen (10) prepared 2-amino-5-hydroxyvaleric acid by acid hydrolysis of ethyl (3-hydroxypropyl)phthalimidomalonate. He invariably obtained proline as byproduct but made no mention of 2-amino-5-valerolactone. Sorensen, however, converted 2-amino-5-hydroxyvaleric acid into proline by heating with hydrochloric acid, which is in agreement

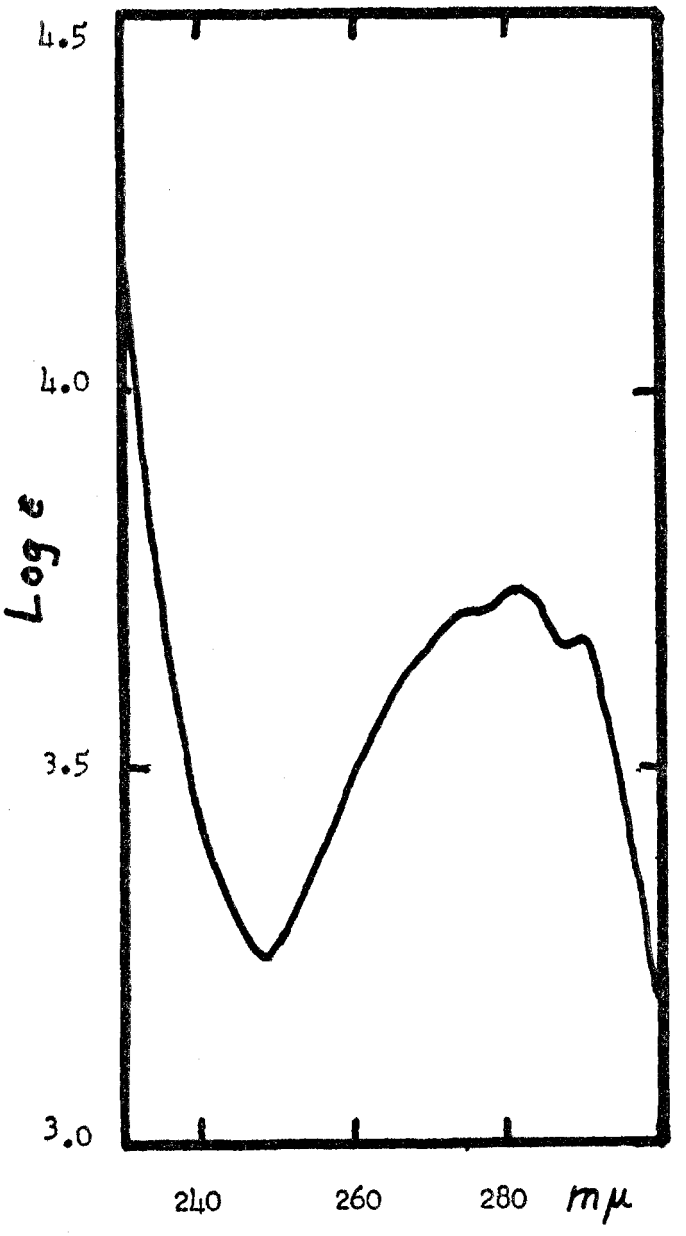


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRAM OF POLYTRYPTOPHAN IN 95% ETHANOL

with a recent communication by Plieninger (11) who cyclized 2-amino-5-hydroxyvaleric acid hydrochloride at 170° to proline hydrochloride. If there were any tendency for the formation of a *delta* lactone in the acid hydrolysis of our polypeptide then it should have given rise to DL-proline, but none was obtained.

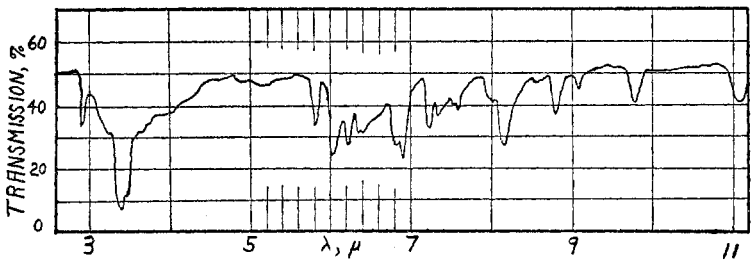


FIG. 2. INFRARED SPECTRUM OF A NUJOL MULL OF THE 152°-PHENYLUREIDO DERIVATIVE OF 2-AMINO-4-HYDROXYVALERIC ACID.

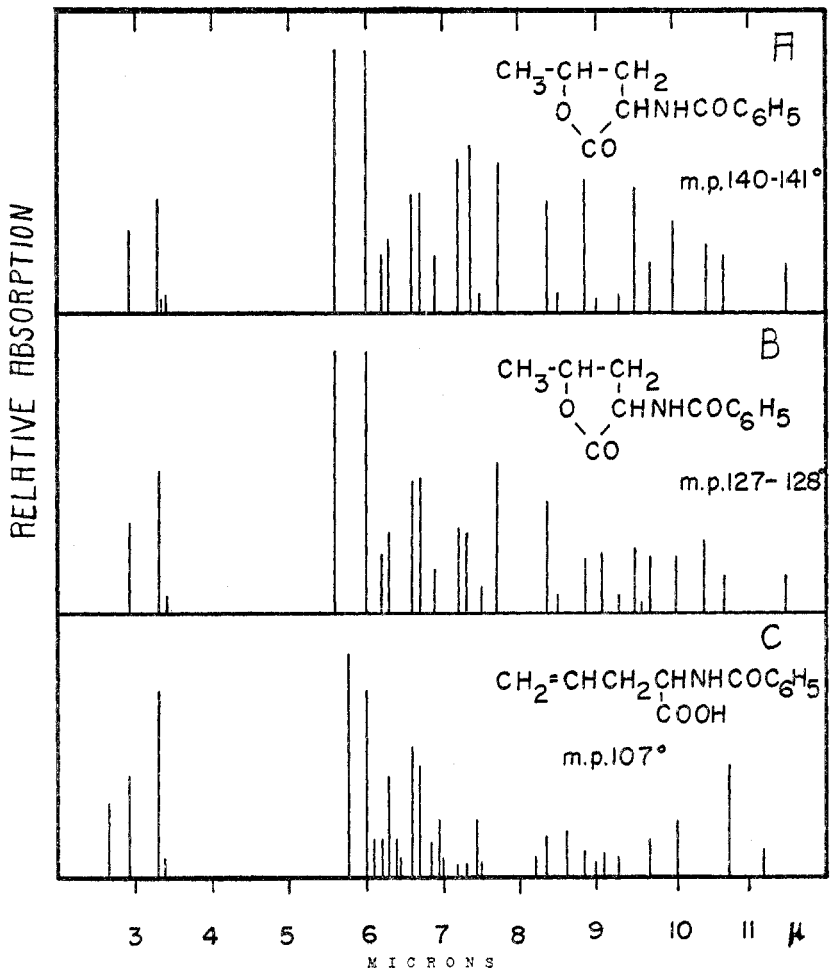


FIG. 3. INFRARED ABSORPTION SPECTRAL LINES OF: (A) Benzoyl derivative (m.p. 140–141°) of 2-amino-4-hydroxyvaleric acid; (B) Benzoyl derivative (m.p. 127–128°) from the 153°-lactone salt; (C) 2-Benzamido-4-pentenoic acid.

Molecular weights of these polypeptides were determined by the modified Van Slyke method (12). Poly-2-amino-4-pentenoic acid, prepared in benzene (see exp. part), gave rise to a volume of nitrogen which indicated a molecular weight of 4100, hence showing about forty repeating amino acid units. Polytryptophan, prepared in benzene, gave a value of 4350 (about 24 units).

TABLE I

MOLECULAR WEIGHTS BY DETERMINATION OF AMINO NITROGEN

SUBSTANCE	MG.	TIME, MIN.	P., MM.	T., °C.	CORR. VOL. OF N_2[d]	N_2 MG.	MOL. WT.
Polytryptophan[a]	41.6	5	749	26	0.491	0.2664	4350
		60	749	26	.606	.3032	3800
Poly-2-amino-4-pentenoic acid[b]	30.8	5	746	26	.406	.2112	4100
		60	746	26	.661	.3357	2550
Polyphenylalanine[b]	53.7	5	750	26	.412	.2158	6800
		60	750	26	.557	.2791	5400
Polyphenylalanine[c]	44.7	5	746	27	1.138	.619	2050
		60	745	26.5	1.412	.754	1650

[a] Prepared in benzene. The substance was dissolved in acetic acid for the determination. [b] Prepared in benzene. Substance taken heterogeneously, in powder form. [c] Prepared in water. Used in powder form. [d] Collected over 50% KOH and corrected by subtracting 0.001 ml. from each 0.100 ml. of nitrogen collected.

EXPERIMENTAL

Sodium ethyl allylmalonate. Ethyl allylmalonate (13) (20 g.) was hydrolyzed with sodium hydroxide (4.0 g.) in ethanol (200 ml.) at 5° for 11 hours, then at 80° for a half-hour. The hot solution was filtered from insoluble material (3.35 g.) and concentrated *in vacuo*. The residue was diluted with ligroin (b.p. 35–60°) to precipitate the salt, which was collected; weight, 12 g. (62%). For analysis the salt was crystallized from ethanol-ligroin, forming colorless needles, m.p. 155° (dec.), the preheated bath being at 150°.

Anal. Calc'd for $C_8H_{11}NaO_4$: Na, 11.87. Found: Na, 11.47.

Disodium allylcarboxyacetohydroxamate. A filtered solution of hydroxylamine (2.5 g.) in ethanol (100 ml.) was added to sodium ethyl allylmalonate (10 g.) dissolved in ethanol (50 ml.) The mixture was treated at 0° with 25 ml. of cold sodium ethoxide solution (1.1 g. of sodium). The salt which separated weighed 9.7 g. (96%).

Anal. Calc'd for $C_6H_7NNa_2O_4$: Na, 22.65. Found: Na, 22.01.

Potassium ethyl allylmalonate. Ethyl allylmalonate (20 g.) was half-hydrolyzed with ethanolic potassium hydroxide solution (5.6 g. in 125 ml.) as above to yield the salt (15 g. or 71%) as colorless rhombs which crystallized from a mixture of ethanol and ligroin (b.p. 35–60°), m.p. 130°.

Anal. Calc'd for $C_8H_{11}KO_4$: K, 18.59. Found: K, 18.84.

Potassium sodium allylcarboxyacetohydroxamate. Hydroxylamine (from 7.0 g. of the hydrochloride) in ethanol (100 ml.) was added to an ethanolic solution of potassium ethyl allylmalonate (15 g. in 25 ml.) and the mixture was treated at 5° with cold sodium ethoxide solution (1.65 g. of sodium in 35 ml. of ethanol). The salt commenced to separate. After 4 hours the mixture was diluted with ligroin (100 ml.) affording 14.6 g. (93%) of the colorless mixed salt.

Allylcarboxyacetohydroxamic acid. A suspension of 1 g. of potassium sodium allylcarboxyacetohydroxamate in ethyl acetate was shaken with the minimum amount of 5 *N* hydrochloric acid until solution occurred. The organic layer was separated and dried with sodium sulfate. Evaporation left a residue of 0.3 g. of the acid which crystallized from ethyl acetate in the form of colorless rhombs. The acid melted at 123° (effervescence) when a sealed tube was plunged into a preheated bath at 120°. The acid was soluble in water and gave an intense violet color with ferric chloride.

Anal. Calc'd for $C_6H_9NO_4$: C, 45.29; H, 5.70; N, 8.80.

Found: C, 45.34; H, 5.60; N, 8.82.

Allylcarboxyaceto(benzoylhydroxamic) acid, $CH_2{=}CHCH_2\underset{\displaystyle COOH}{\underset{|}{C}}HCONH{-}OCOC_6H_5$. An aqueous solution of potassium sodium allylcarboxyacetohydroxamate (4.4 g. in 40 ml.) was benzoylated at 5° by stirring with 2.8 ml. of benzoyl chloride for 15 minutes. Alkali was added as needed to maintain slight alkalinity. Then, 1.0 ml. more of benzoyl chloride was added. After another half hour of stirring, 75 ml. of ethyl acetate was added. Then the mixture was acidified in the cold with concentrated hydrochloric acid, and the organic layer was separated and evaporated yielding allylcarboxyaceto(benzoylhydroxamic) acid. After crystallization from benzene it weighed 3.9 g. (73%). For analysis the material was recrystallized from benzene or chloroform and was obtained as colorless prismatic needles, m.p. 125° (dec. in a sealed tube) with preheated bath at 120°.

Anal. Calc'd for $C_{13}H_{13}NO_5$: C, 59.30; H, 4.97; N, 5.32.

Found: C, 59.82; H, 5.28; N, 5.64.

Benzoylation of the disodium salt (6.0 g.) as described above gave 4.25 g. (54%) of pure allylcarboxyaceto(benzoylhydroxamic) acid.

Sodium allylcarboxyaceto(benzoylhydroxamate). An ethanolic solution of the acid (4.88 g.) was treated with an equivalent amount of sodium ethoxide (total, 20 ml. of ethanol). The salt precipitated as a gel and was covered with dry ether (10 ml.) and ligroin (b.p. 35–60°; 100 ml.). These solvents helped to form a more crystalline precipitate which filtered easily. After drying *in vacuo* over phosphoric anhydride and paraffin wax the salt weighed 4.77 g. (90%).

Anal. Calc'd for $C_{13}H_{12}NNaO_5$: Na, 8.07. Found: Na, 8.44.

Rearrangement of sodium allylcarboxyaceto(benzoylhydroxamate). (*a*) *In ethanol.* The sodium salt was prepared *in situ* by treating a solution of the acid (2.7 g.) in ethanol (50 ml.) with sodium ethoxide solution (0.23 g. of sodium in 5 ml. of ethanol). The mixture was refluxed (oil-bath at 100°) for two hours. Hydrochloric acid (25 ml. of 10 *N*) was then added and refluxing was continued for two hours longer. The solution was then concentrated to a small bulk in a dry air stream, cooled, filtered from sodium chloride, and evaporated to dryness. The residue was desiccated *in vacuo* over alkali. The gum refused to crystallize, hence it was dissolved in cold sodium hydroxide solution, filtered, and shaken with benzoyl chloride (2 ml.). The alkaline solution was extracted with ether, acidified, and re-extracted with ether. After removing ether, the gummy residual acid was dissolved in hot benzene. Addition of ligroin (b.p. 35–60°) precipitated an oil which was redissolved in fresh benzene and once more precipitated with ligroin (b.p. 86–100°). This gum was taken up in benzene and allowed to stand when the solution deposited colorless crystals of 2-benzamido-4-pentenoic acid (0.31 g.) of m.p. 107° [literature (14), 107–107.5°].

(*b*) *In water.* An aqueous solution of the salt (2.85 g. in 30 ml.) was heated on the steam-bath for two hours. The gelatinous polypeptide was collected on a filter and dried *in vacuo*. The weight was 0.55 g. or 57% based on $[{-}NHCH(CH_2CH{=}CH_2)CO{-}]_n$.

The polypeptide (0.53 g.) was boiled with ethanol (25 ml.) for 30 minutes, filtered hot, and then boiled with toluene (25 ml.) for 15 minutes and again filtered hot. The dry insoluble material weighed 0.41 g. It gave a ninhydrin test by adsorption.

For analysis the polypeptide was dissolved in anhydrous formic acid (totally soluble) and precipitated on cooling with two volumes of water and dried at 150° (1 mm.) for 4 hours.

When heated in a capillary tube, the product melted somewhat and decomposed by 300°, but it was not totally liquid by 360°.

Anal. Calc'd for $(C_5H_7NO)_n$: C, 61.80; H, 7.26; N, 14.42.
Found: C, 59.93; H, 7.23; N, 13.77.

A solution of the polypeptide in formic acid decolorized bromine in acetic acid.

Rearrangement of another batch of sodium salt in water (2.85 g. in 15 ml.) as above gave 0.86 g. (88%) of the polypeptide.

(*c*) *In benzene.* A suspension of the sodium salt in dry benzene (1.82 g. in 25 ml.) was refluxed for two hours, filtered hot, dried, and triturated with water (25 ml.) for one hour. The solid polypeptide (0.57 g. or 92%) was collected. The benzene filtrate contained a negligible amount of material.

The polypeptide (0.55 g.) after extraction with boiling ethanol and toluene as above, weighed 0.47 g. and was dried for analysis as above.

Anal. Calc'd for $(C_5H_7NO)_n$: C, 61.80; H, 7.26; N, 14.42.
Found: C, 60.57; H, 6.69; N, 14.36.

The polypeptide when boiled with anhydrous formic acid was only about half soluble. On cooling, after filtration, the product was precipitated by two volumes of water. The gelatinous polypeptide was separated and boiled with toluene. Toluene was removed by filtration and the product was dried for analysis, *in vacuo*, as above. The polymer had turned black by 360°. It decomposed without melting.

Anal. Found: C, 61.11; H, 7.35; N, 14.28.

Hydrolysis of poly-2-amino-4-pentenoic acid (from benzene rearrangement). The polypeptide (1 g.) was heated with concentrated hydrochloric acid (10 ml.) at 130–140° for five hours. The light brown solution so obtained was boiled with Norit, filtered, and evaporated to dryness. The semi-solid was boiled with 2-propanol (20 ml.) and filtered hot. The insoluble product (0.41 g.) melted at 189°. The filtrate afforded an additional crop (0.35 g.), m.p. 179–183°. Recrystallization of either fraction first from 2-propanol and then from ethanol yielded colorless prisms, m.p. 192–193°, which identifies this product (A) as 2-amino-4-valerolactone hydrochloride, lit. m.p. 194–196° (4, 8). The yield was 50% calculated from the polypeptide.

Anal. Calc'd for $C_5H_{10}ClNO_2$: N, 9.24. Found: N, 9.58.

The mother liquor was concentrated to small bulk and another hydrochloride (B) (0.14 g. or 9%) was obtained which crystallized from 2-propanol in clusters of colorless prisms, m.p. 153°.

Anal. Calc'd for $C_5H_{10}ClNO_2$: C, 39.62; H, 6.64; N, 9.24.
Found: C, 39.72; H, 6.77; N, 9.23.

Derivative of (A). Benzoyl derivative. A solution of the hydrochloride (0.3 g.) in cold sodium hydroxide solution (8 ml. of 0.5 *N*) was reacted with benzoyl chloride (0.5 ml.) for one hour. The alkaline solution was then extracted with ether to remove excess benzoyl chloride, acidified, and re-extracted with ether. The ether solution was evaporated in an air stream on the steam-bath and the residue was dried *in vacuo* for three hours. The latter was boiled with ligroin (b.p. 35–60° and then b.p. 86–100°) to remove benzoic acid. The insoluble residue crystallized in colorless rhombs from benzene to constant m.p. 136°. The melting point was not raised on crystallization from chloroform-ligroin. However, if the product was just melted, solidified, and recrystallized from benzene the melting point was raised to 140–141°, which is in agreement with the m.p. in the literature for 2-benzamido-4-valerolactone (4, 7, 8).

Anal. Calc'd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.98; N, 6.39.
Found: C, 65.99; H, 6.01; N, 6.51.

Phenylureido derivative. A solution of the hydrochloride in 0.5 *N* sodium hydroxide solution (0.25 g. in 8 ml.) was treated with phenyl isocyanate (0.5 ml.) at 0° and the mixture was allowed to stand for two hours at 0–20°. Diphenylurea was filtered off and the alkaline solution was acidified at 0°. The solid was filtered, crystallized first from water, then from ethyl acetate in colorless prisms, m.p. 152° (from both solvents).

Anal. Calc'd for $C_{12}H_{16}N_2O_4$: C, 57.12; H, 6.39; N, 11.11.
Found: C, 57.16; H, 6.47; N, 11.16.

Benzoyl derivative of (B). The hydrochloride (0.1 g.) was dissolved in 0.5 *N* sodium hydroxide solution (5 ml.) and treated with benzoyl chloride (0.2 ml.) for two hours and worked up as for the benzoyl derivative of (A). Crystallization of the residue (after extraction with ligroin) from benzene and ligroin (b.p. 86–100°) yielded colorless prisms, m.p. 127–128°.

Anal. Calc'd. for $C_{12}H_{13}NO_3$: N, 6.39. Found: N, 6.46.

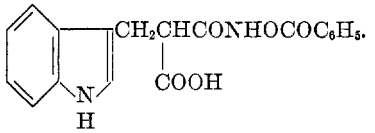
Ethyl 3-indolylmethylmalonate. This ester was made following procedures used by Snyder (15) for related tryptophan compounds. Briefly, gramine (17.5 g.), ethyl malonate (20 g.), and powdered sodium hydroxide (1.2 g.) were refluxed in toluene in an atmosphere of nitrogen for three hours. The solution was filtered and the toluene was evaporated in a stream of nitrogen; excess malonic ester was removed by keeping the residue at 100° under 1 mm. for two hours. The mixture was cooled, taken up in 95% ethanol (30 ml.), and slowly precipitated by water (10 ml.). Seeding and scratching gave the ester (25 g.; 86%) m.p. 56–58°. Snyder reported m.p. 62°.

Sodium ethyl 3-indolylmethylmalonate. A solution of the malonic ester (25 g.) in ethanolic sodium hydroxide (4 g. in 250 ml.) was set aside for 8 hours at 5°. The solid (5 g.) which separated was filtered off. The filtrate was evaporated on a steam-bath in a stream of nitrogen. The residual gum was triturated with dry ether and left overnight. The salt crystallized and was collected (17.6 g. or 72%). A sample for analysis was recrystallized from a little ethanol and dry ether. It appeared as colorless needles, which sintered at 120° and decomposed to a brown liquid at 146°.

Anal. Calc'd for $C_{14}H_{14}NNaO_4$: N, 4.95. Found: N, 4.89.

Treatment of sodium ethyl 3-indolylmethylmalonate (17.6 g.) with ethanolic hydroxylamine solution (from 7 g. of the hydrochloride) as described above, followed by sodium ethoxide (1.43 g. of sodium in 35 ml. of ethanol) gave disodium α-carboxy-β-3-indolylpropionohydroxamate, analogous to the above disodium allylcarboxyacetohydroxamate. The salt weighed 16.5 g. (91%).

α-Carboxy-β-3-indolylpropiono(benzoylhydroxamic) acid,



Benzoylation of disodium α-carboxy-β-3-indolylpropionohydroxamate (2.92 g.) in aqueous sodium acetate solution (1.36 g. in 15 ml.), in the manner described above, afforded α-carboxy-β-3-indolylpropiono(benzoylhydroxamic) acid. Recrystallization with Norit from a mixture of ethyl acetate and benzene afforded buff needles, m.p. 143° (dec.). Several additional recrystallizations gave white needles, m.p. 146–147° (dec.).

Anal. Calc'd for $C_{19}H_{18}N_2O_5$: C, 64.78; H, 4.57; N, 7.95.
Found: C, 64.82; H, 4.69; N, 8.03.

The sodium salt of this acid was prepared, as described above for the analogous compounds, by treating a cold alcohol solution of the acid with one molar equivalent of sodium ethoxide.

Rearrangement of sodium α-carboxy-β-3-indolylpropiono(benzoylhydroxamate). (*a*) *In water.* An aqueous solution of the salt (1.8 g. in 10 ml. of water) was heated on the steam-bath for 0.5 hour. A gummy solid separated. The mixture was cooled, the water decanted, and the gum dissolved in ethanol. Addition of water caused formation of a colloidal solution which was easily flocculated with ammonium sulfate or potassium nitrate solution. The polymer was filtered, dried, and weighed 0.67 g. (72%). When heated in a capillary tube it decomposed around 200°. For analysis the material was recrystallized from aqueous ethanol and dried at 150° (1 mm.) for 4 hours. It was soluble in acetone or acetic acid as well as alcohol.

Anal. Calc'd for $(C_{11}H_{10}N_2O)_n$: C, 70.95; H, 5.41; N, 15.05.
Found: C, 69.31; H, 5.59; N, 14.08, 14.12.

(*b*) *In benzene.* A suspension of the salt (3.74 g.) in dry benzene (30 ml.) was boiled for three hours, cooled, and filtered. The insoluble material was triturated with water (30 ml.)

and the polytryptophan was collected. The yield was 1.8 g. (96%). The solid was completely soluble in ethanol, acetone, and acetic acid. As with the polymer formed in (*a*), a colloidal solution was formed on adding water to an alcohol solution, and this colloid was coagulated by salts. For analysis, the substance was recrystallized from aqueous ethanol and dried as described above.

Anal. Calc'd for $(C_{11}H_{10}N_2O)_n$: C, 70.95; H, 5.41; N, 15.05.
Found: C, 71.04; H, 5.73; N, 15.14.

Molecular weights. Dr. John E. Maurer of this laboratory assisted in these determinations. The modified Van Slyke method (12) was used. Data for the two polypeptides are shown in Table I, and polyphenylalanine is included for comparison. The 5-minute values are taken as a close approximation of the molecular weight, and the 60-minute values show that some breakdown of the polypeptides occurs in this period, as would be expected.

Acknowledgments. Microanalyses for C, H, and N were carried out by Miss J. Sorensen and Mrs. C. White. Infrared curves were obtained by Miss R. Guy. One of us (L. B.) received a travel grant from the New South Wales Branch of Royal Australian Chemical Institute, and also a grant-in-aid of research from Swift and Company without which help this work could not have been performed.

SUMMARY

Allylcarboxyaceto(benzoylhydroxamic) acid and α-carboxy-β-3-indolylpropiono(benzoylhydroxamic) acid were synthesized and from them were prepared poly-2-amino-4-pentenoic acid and polytryptophan. Acid hydrolysis of the first of these polypeptides gave rise to two different racemic forms of 2-amino-4-valerolactone hydrochloride, only one of which had been previously described. Various physical and chemical properties of these substances are listed.

EVANSTON, ILLINOIS

REFERENCES

(1) (a) HURD AND BUESS, *J. Am. Chem. Soc.*, **73**, 2409 (1951); (b) HURD AND BAUER, *J. Am. Chem. Soc.*, **73**, 4387 (1951).
(2) HURD, BAUER, AND KLOTZ, *J. Am. Chem. Soc.*, **75**, 624 (1953).
(3) Recent articles on the Leuchs method for preparing polypeptides are: PETRI AND STAVERMAN, *Rec. trav. chim.*, **71**, 385 (1952); PARROD, *Bull. soc. chim.*, **18**, 420 (1951).
(4) GOERING, CRISTOL, AND DITTMER, *J. Am. Chem. Soc.*, **70**, 3310 (1948).
(5) EDWARDS, *Arch. Biochem.*, **21**, 103 (1949); DANNENBERG, *Angew. Chem.*, **63**, 208 (1951).
(6) LINSTEAD AND RYDON, *J. Chem. Soc.*, 580 (1933).
(7) FILLMAN AND ALBERTSON, *J. Am. Chem. Soc.*, **70**, 171 (1948).
(8) FISCHER AND LEUCHS, *Ber.*, **35**, 3787 (1902).
(9) ALBERTSON AND FILLMAN, *J. Am. Chem. Soc.*, **71**, 2818 (1949). We are indebted to Dr. Albertson for a sample of this material for the mixture m.p. determination.
(10) SORENSEN, *Chem. Zentr.*, **II**, 398 (1905); SORENSEN AND ANDERSEN, *Chem. Zentr.*, **II**, 684 (1908).
(11) PLIENINGER, *Chem. Ber.*, **83**, 271 (1950).
(12) HUSSEY AND MAURER, *Anal. Chem.*, **24**, 1642 (1952).
(13) MANNICH AND REITSERT, *Ber.*, **57**, 1116 (1924), mentioned ethyl hydrogen allylmalonate but did not report its mode of preparation nor its alkali salts.
(14) SORENSEN, *Ber.*, **41**, 3388 (1908); KARRER AND SCHNEIDER, *Helv. Chim. Acta.*, **13**, 1281 (1930).
(15) SNYDER AND CO-WORKERS, *J. Am. Chem. Soc.*, **66**, 200 (1944); **67**, 38 (1945); **70**, 3788 (1948).