[CONTRIBUTION FROM THE RESEARCH DEPARTMENT, CALCO CHEMICAL DIVISION, AMERICAN CYANAMID COMPANY]

Analogs of Pteroylglutamic Acid. IV. Replacement of Glutamic Acid by Other Amino Acids

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Variations in the structure of pteroylglutamic acid (I)[2] have given substances of widespread interest. Hutchings, *et al.*,[3] synthesized pteroylaspartic acid, the first analog of pteroylglutamic acid to be isolated in pure form and adequately characterized. It showed pteroylglutamic acid antagonist activity in a number of species. Previous communications from this Laboratory described the synthesis of the N^{10}-alkyl,[4] 4-amino[5] and 9-methyl[6] derivatives of pteroylglutamic acid. The present paper describes a number of analogs prepared for preliminary screening experiments in which the glutamic acid moiety is replaced by other amino acids. Also described are some of the corresponding 4-aminopteroyl derivatives which contain an amino group in the 4-position of the pteridine ring.

Synthesis was accomplished by the method of Waller, *et al.*,[7] in which 2,4,5-triamino-6-hydroxypyrimidine, 2,3-dibromopropionaldehyde, and the N-(*p*-aminobenzoyl)-amino acid are brought together in water at an acid *p*H. For the 4-amino derivatives,[5] 2,4,5,6-tetraminopyrimidine[8] was substituted for the triaminohydroxypyrimidine. Usually one-half equivalent of iodine or sodium dichromate was added during the condensation.

TABLE I

N-(*p*-NITROBENZOYL)-AMINO ACIDS, NO_2—C(=O)—R

R = Amino acid	Recrystallization solvent	M. p., °C. (cor.)	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
β-Alanine	Water	163.8–165.0	77	$C_{10}H_{10}N_2O_5$	50.41	50.4	4.23	4.23	11.76	11.5
ε-Aminocaproic acid	Dilute alcohol	147.5–148.5	67	$C_{13}H_{16}N_2O_5$	55.71	55.6	5.76	5.94	10.00	10.1
Diethyl aminomalonate	Alcohol	135–136	60	$C_{14}H_{16}N_2O_7$	51.85	52.1	4.97	4.80	8.64	8.71
Isoleucine (*dl*)	Dilute alcohol	186–187	74	$C_{13}H_{16}N_2O_5$	55.71	55.6	5.76	5.61	10.00	10.1
Methionine (*dl*)	Dilute alcohol	170–171	62	$C_{12}H_{14}N_2O_5S$[a]	48.30	48.6	4.73	4.68	9.40	9.61
Sarcosine	Water	140–141	71	$C_{10}H_{10}N_2O_5$	50.41	50.3	4.23	4.40	11.76	11.6
Tryptophan (*dl*)	Dilute alcohol	196.5–197.5	40	$C_{18}H_{15}N_3O_5$	61.16	60.9	4.28	4.18	11.90	12.3

[a] Calcd.: S, 10.75. Found: S, 10.7.

TABLE II

N-(*p*-AMINOBENZOYL)-AMINO ACIDS, NH_2—C(=O)—R

R = Amino acid	M. p., °C. (cor.)	Yield, %	Formula	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Nitrogen Calcd.	Nitrogen Found
Alanine (*dl*)[a]	192.5–194.0	75	$C_{10}H_{12}N_2O_3$	57.67	57.6	5.81	5.84	13.46	13.6
β-Alanine[f]	151.8–153.2	60.5	$C_{10}H_{12}N_2O_3$	57.67	57.6	5.81	5.8	13.46	13.3
ε-Aminocaproic acid	132.0–133.0	80	$C_{13}H_{18}N_2O_3$	62.39	62.4	7.25	7.15	11.20	11.2
Aminomalonic acid·H_2O	150 (decarb.)	99	$C_{10}H_{12}N_2O_6$	46.86	46.6	4.72	5.00	10.94	11.0
Diethyl ester	122.0–123.0	93	$C_{14}H_{18}N_2O_5$	57.15	57.2	6.16	6.23	9.52	9.53
Isoleucine (*dl*)	189.0–191.0	85	$C_{13}H_{18}N_2O_3$	62.39	62.7	7.25	7.54	11.20	11.2
Phenylalanine (*dl*)[b]	195.0–196.0	70	$C_{16}H_{16}N_2O_3$	67.56	67.3	5.67	5.82	9.86	9.67
Serine (*dl*)[c]	192[d]	91	$C_{10}H_{12}N_2O_4$	53.55	53.8	5.40	5.50	12.50	12.6
Threonine (*dl*)[d]	192.0–193.0	45	$C_{11}H_{14}N_2O_4$	55.44	55.7	5.92	6.20	11.76	11.8
Tryptophan (*dl*)	199.0–201.0	92	$C_{18}H_{17}N_3O_3$	66.85	66.8	5.30	5.34	13.00	13.2
Valine (*dl*)[e]	196.0–197.0	55	$C_{12}H_{16}N_2O_3$	61.00	61.3	6.83	6.73	11.86	11.8

[a] N-(*p*-Nitrobenzoyl) derivative, m. p. 192.5–194°; Colles and Gibson, *J. Chem. Soc.*, 101 (1928). [b] N-(*p*-Nitrobenzoyl) derivative, m. p. 169.5–170°; Karrer and Christoffel, *Helv. Chim. Acta*, **27**, 623 (1944). [c] N-(*p*-Nitrobenzoyl) derivative, m. p. 195.5–196.0°; Ross and Green, *J. Biol. Chem.*, **137**, 110 (1941); Fischer and Jacobs, *Ber.*, **39**, 2943 (1906). [d] N-(*p*-Nitrobenzoyl) derivative, Siro Maeda, *et al.*, *C. A.*, **33**, 2948 (1939). [e] N-(*p*-Nitrobenzoyl) derivative, m. p. 170–172°; ref. (*b*) above.. [f] Prepared by zinc and acid reduction.

(1) Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

(2) Angier, *et al.*, *Science*, **103**, 667 (1946).

(3) Hutchings, *et al.*, *J. Biol. Chem.*, **170**, 323 (1947).

(4) Cosulich and Smith, THIS JOURNAL, **70**, 1922 (1948).

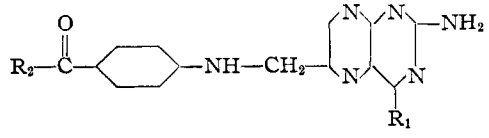
(5) Seeger, Smith and Hultquist, *ibid.*, **69**, 2567 (1947).

(6) Hultquist, Smith, Seeger, Cosulich and Kuh, *ibid.*, **71**, 619 (1949).

(7) Waller, *et al.*, *ibid.*, **70**, 19 (1948).

(8) Traube, *Ber.*, **37**, 4545 (1904).

In certain cases 1,1,3-tribromoacetone,[9a] the tetraminopyrimidine, and N-(*p*-aminobenzoyl)-amino acid were used, in a modification of the method of Hultquist and Dreisbach.[9b] The following were purified by methods similar to those described for pteroylglutamic acid and its analogs[6,9,10]: pteroylalanine (II), pteroyl-β-alanine (III), pteramidomalonic acid (IV), 4-aminopteramidomalonic acid (V), and 4-aminopteroylserine (VI). The remainder of the analogs described herein were examined as the crude reaction products (see Table III).



R_1 = OH I, R_2 = —NHCH(COOH)CH_2CH_2COOH
II, R_2 = —NHCH(CH_3)COOH
III, R_2 = —NHCH_2CH_2COOH
IV, R_2 = —NHCH(COOH)$_2$
R_1 = —NH_2 V, R_2 = —NHCH(COOH)$_2$
VI, R_2 = —NHCH(CH_2OH)COOH

In the course of this work a number of N-(*p*-nitrobenzoyl)-amino acids and N-(*p*-aminobenzoyl)-amino acids were prepared which have not been reported in the literature. Data on these compounds are given in Tables I and II.

The biological properties of these pteroylglutamic acid derivatives have been examined by Dr. E. L. R. Stokstad and Dr. B. L. Hutchings of the Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York. The details of this work will be published elsewhere.

Experimental

N-(*p*-Nitrobenzoyl)-amino Acids.—The serine and threonine derivatives were prepared by the method of Fischer and Jacobs.[11]

The other compounds were prepared as described below. One-tenth mole of the amino acid and 0.2 mole of 1*N* sodium hydroxide solution were mixed and cooled to 0–10°. One-tenth mole of *p*-nitrobenzoyl chloride was added and the mixture was stirred at 0–10° for one-half hour and then allowed to warm slowly to room temperature. The total reaction time was one and one-half to three hours. The unreacted *p*-nitrobenzoyl chloride was filtered off. The filtrate was cooled in an ice-bath as dilute acid was added until the mixture was at *p*H 2–3. After additional cooling, the product was filtered, washed with water, and dried overnight at 50–60°. The crude products were purified by recrystallization from the solvents indicated. An initial extraction with boiling ether removed much of the impurity from the alanine, phenylalanine and ε-aminocaproic acid derivatives.

In the case of cystine, 0.4 mole of 1*N* sodium hydroxide and 0.2 mole of *p*-nitrobenzoyl chloride were used and the bis derivative was obtained. The product was insoluble in alcohol and was purified by dissolving with cold dilute alkali, treating with Darco, and precipitating by addition of dilute acid (see Table I).

N-(*p*-Aminobenzoyl)-amino Acids.—The N-(*p*-nitrobenzoyl)-amino acids in alcohol solution were reduced catalytically using palladium on activated charcoal as a catalyst (see Table II).

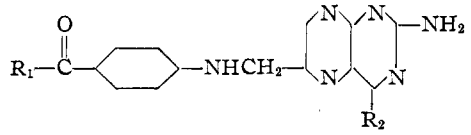
The N-(*p*-aminobenzoyl) derivatives of cystine, methionine and sarcosine were not isolated and characterized. The reduction solution was used directly in the reaction with dibromopropionaldehyde and 2,4,5-triamino-6-hydroxypyrimidine (see Table III).

Diethyl *p*-Nitrobenzamidomalonate.—Diethyl isonitrosomalonate was prepared in 82% yield, and reduced to diethyl aminomalonate by the method of Cerchez.[12] The product was treated directly without isolation with *p*-nitrobenzoyl chloride in a modification of the method of Redemann and Dunn[13] for the preparation of diethyl benzamidomalonate. An example of our procedure is described in detail below.

To 200 g. (1.06 moles) of diethyl isonitrosomalonate dissolved in 1600 ml. of ether was added the aluminum amalgam prepared from 48 g. of aluminum foil. Efficient cooling with an ice-bath was required to control the initial reaction. When the reaction had subsided, 300 ml. of water was added dropwise over a five-hour period to the refluxing mixture. The mixture was filtered and the precipitate washed with ether. To the combined filtrates were added 100 g. of pyridine and 500 ml. of water. A solution of 110 g. (0.6 mole) of *p*-nitrobenzoyl chloride in 400 ml. of ether was then added over a one-half hour period at reflux temperature. After heating under reflux for one hour longer, 1000 ml. of water was added, and the precipitate was filtered. It was recrystallized once from 1400 ml. of 2B alcohol to yield 83 g. (24%) of diethyl *p*-nitrobenzamidomalonate which melted at 135.5–136.5°. The ether layer was washed with water and then combined

TABLE III

PTEROYL AND 4-AMINOPTEROYLAMINO ACIDS,



	R_2 = OH		R_2 = NH_2	
R_1	Purity,[a] %	Biological activity,[b] %	Purity,[a] %	Biological activity,[b] %
Alanine (*dl*)	Analytical	0[c]		
Alanine (*dl*)	20.7	0	14.5	0
β-Alanine	Analytical	+2.46		
ε-Aminocaproic acid	27.0	0	11.5	.....
Aminomalonic acid	Analytical	+0.007	66.4	−0.1
Aminomalonic acid	17.4	0	14.0	.....
Cystine (*l*) (*bis*)[d]	22.5	0		
Isoleucine (*dl*)	8.7	.....	5.4	.....
Methionine	25.0	+		
Phenylalanine (*dl*)	13.0	0	5.5	.....
Sarcosine	20.4	+	18.3	.....
Serine (*dl*)			Analytical	−0.174
Serine (*dl*)	18.3	0	22.8	.....
Threonine·H_2O (*dl*)	19.0	.....	22.4	.....
Tryptophan (*dl*)	7.8	.....	8.3	.....
Valine (*dl*)	13.8	0	11.0	0

[a] "Analytical" denotes an analytically pure sample. Per cent. values were determined by the chemical assay method of Hutchings, *et al.* (see ref. 14), and have been corrected for an inert diluent (barium sulfate) present in the crudes. [b] Determined for *S. faecalis* R; + = growth activity as compared to pteroylglutamic acid at 100; — = antagonist activity of N^{10}-methylpteroylglutamic acid for half-maximum inhibition of the growth of *Streptococcus faecalis* R. Values for other compounds are reported in terms of the standard. See ref. 3. [c] 0 = no activity, either as growth-promoter or antagonist. [d] bis-N-(*p*-Nitrobenzoyl)-cystine, Yoshikuni Inoue, *C.A.*, **24**, 341 (1930).

(9) (a) Watson and Yates, *J. Chem. Soc.*, 1207 (1932); (b) Hultquist and Dreisbach, U. S. Patent 2,443,165 (1948).

(10) Stokstad, *et al.*, THIS JOURNAL, **70**, 8 (1948); Mowat, *et al.*, *ibid.*, **70**, 1097 (1948).

(11) Fischer and Jacobs, *Ber.*, **39**, 2942 (1906).

(12) Cerchez, *Bull. soc. chim.*, [4] **47**, 1279 (1930).

(13) Redemann and Dunn, *J. Biol. Chem.*, **130**, 341 (1939).

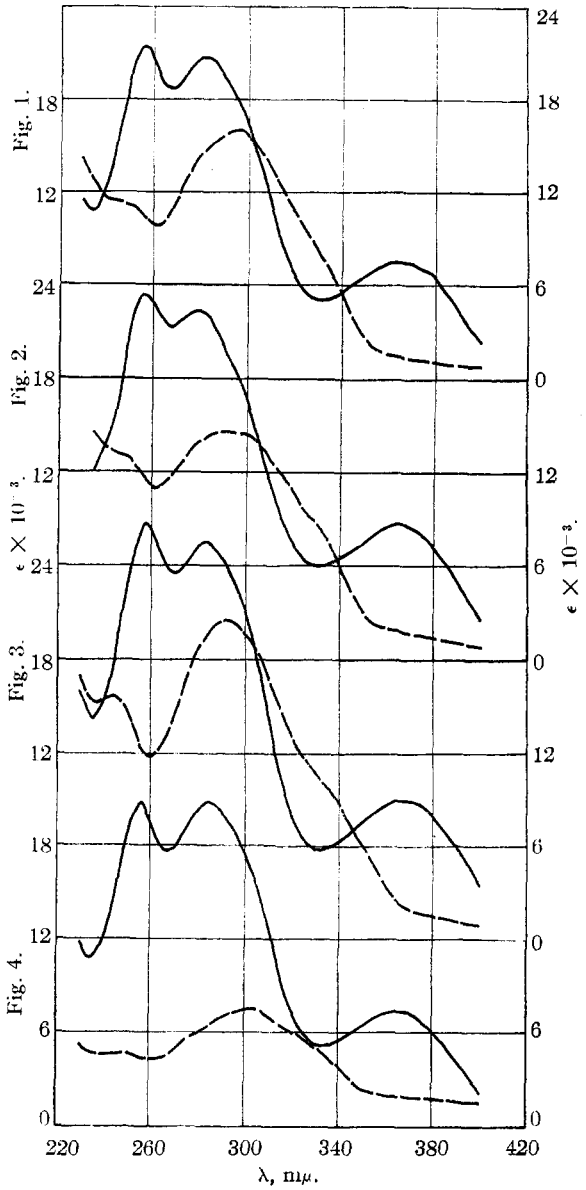


Fig. 1.—Ultraviolet absorption spectra[a] of pteroylalanine: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

Fig. 2.—Ultraviolet absorption spectra[a] of pteroyl-β-alanine: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

Fig. 3.—Ultraviolet absorption spectra[a] of 4-aminopteroylserine: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

Fig. 4.—Ultraviolet absorption spectra[a] of pteramidomalonic acid: ——— in 0.1 *N* sodium hydroxide; ---------- in 0.1 *N* hydrochloric acid.

[a] ε is the molecular extinction coefficient as defined by $I = I_0 10^{-\varepsilon cl}$ where c is the concentration in moles/liter and l is the cell length in centimeters. Transmittancy (I/I_0) measurements of 10 mg./l. solutions were made in 1 cm. cell at mμ intervals on a Model DU Beckman spectrophotometer using a solvent filled cell in the reference position. Additional data were obtained at 2 mμ intervals at maxima, minima and points of inflection.

with the above alcohol filtrate. Evaporation until precipitation began yielded an additional 60 g. (18%) which melted at 132.0–135.0°.

Anal. Calcd. for $C_{14}H_{16}N_2O_7$: C, 51.85; H, 4.97; N, 8.64. Found: C, 52.1; H, 4.80; N, 8.71.

Diethyl *p*-Aminobenzamidomalonate.—Catalytic hydrogenation of 9.72 g. (0.03 mole) of diethyl *p*-nitrobenzamidomalonate suspended in 200 ml. of 2B alcohol, using a palladium on activated charcoal catalyst, yielded 8.2 g. (93%) of diethyl *p*-aminobenzamidomalonate in the form of long white needles which melted at 122–123°.

Anal. Calcd. for $C_{14}H_{18}N_2O_5$: C, 57.15; H, 6.16; N, 9.52. Found: C, 57.2; H, 6.23; N, 9.53.

***p*-Aminobenzamidomalonic Acid.**—A mixture of 5.88 g. (0.02 mole) of diethyl *p*-aminobenzamidomalonate and 50 ml. (0.10 mole) of 2 *N* sodium hydroxide solution was stirred for two hours. The reaction was acidified with 50 ml. (0.10 mole) of 2 *N* hydrochloric acid, cooled in an ice-bath for three hours, filtered, and the precipitate dried overnight at 40°. The product, 4.7 g. (99%), was almost insoluble in water, alcohol, acetone and ether. A portion which was redissolved in *N* sodium hydroxide solution, filtered, acidified with *N* hydrochloric acid and allowed to stand at room temperature precipitated as clusters of white needles. These were dried for analysis at room temperature in vacuum over phosphorus pentoxide. The dried sample contained one mole of water of crystallization, lost water or decarboxylated at about 150°, and did not melt completely at 250°.

Anal. Calcd. for $C_{10}H_{10}N_2O_5 \cdot H_2O$: C, 46.86; H, 4.72; N, 10.94; H_2O, 7.04. Found: C, 46.6; H, 5.00; N, 11.0; H_2O, 8.08.

Pteroylalanine (II).—Pteroylalanine was prepared by a modification of the method of Waller[7] from 2,4,5-triamino-6-hydroxypyrimidine, 2,3-dibromopropionaldehyde, and N-(*p*-aminobenzoyl)-alanine; 0.5 equivalent of iodine or sodium dichromate was added as oxidant during the condensation. Pteroylalanine was purified and isolated as the magnesium salt by known methods[6,9b,10] (see Table III).

Anal. Calcd. for $C_{17}H_{15}N_7O_4Mg \cdot H_2O$: C, 48.19; H, 4.04; N, 23.15; Mg, 5.74. Found: C, 48.6; H, 3.69; N, 23.5; Mg, 5.89.

Pteroyl-β-alanine (III).—This compound was prepared from N-(*p*-aminobenzoyl)-β-alanine by the method of Waller,[7] modified as for II above, and purified by known methods.[6,9b,10] The purity was 77.9% by chemical assay.[14] Final purification was accomplished as follows: The sample (400 mg.) was dissolved in 10 ml. of dilute sodium hydroxide; the sodium salt was precipitated by the addition of 10 ml. of 10 *N* sodium hydroxide. The crystalline sodium salt was filtered off and recrystallized from 40 ml. of 5 *N* sodium hydroxide. It was converted to the free acid by solution in 20 ml. of water, acidification with 5 ml. of concentrated hydrochloric acid, and dilution to 40 ml. volume. The product which was filtered off was recrystallized by dissolving in 10 ml. of 6 *N* hydrochloric acid and diluting to 35 ml. The final product was collected, washed with water, alcohol and ether and dried fifteen hours at 100° (1 mm.). The purity by chemical assay was 98% (see Table III).

Anal. Calcd. for $C_{17}H_{17}O_4N_7$: C, 53.3; H, 4.44; N, 25.6. Found: C, 52.94; H, 4.74; N, 25.30.

Pteramidomalonic Acid (IV).—This compound was prepared from *p*-aminobenzamidomalonic acid by the method of Waller,[7] modified as for II above and purified and characterized as the magnesium salt by known methods.[6,9b,10]

Anal. Calcd. for $C_{17}H_{12}N_7O_6Mg_{1.5} \cdot 2H_2O$: C, 42.29; H, 3.34; N, 20.32; Mg, 7.56. Found: C, 42.0; H, 3.56; N, 20.4; Mg, 7.78.

4-Aminopteramidomalonic Acid (V).—This compound was prepared by the method of Waller, *et al.*,[7] from 2,4,5,6-tetraaminopyrimidine, 2,3-dibromopropionaldehyde, and

(14) Hutchings, *et al.*, *J. Biol. Chem.*, **168**, 705 (1947).

p-aminobenzamidomalonic acid, modified as for II above (see Table III). Also, V was synthesized by a variation of the procedure employed by Hultquist and Dreisbach using 1,1,3-tribromoacetone.[9] The crude product prepared by the latter method contained about 30% of the desired compound, as estimated by the chemical assay of Hutchings, *et al.*[14] The crude was dissolved in 5% sodium carbonate solution at a concentration of 6 g. of V per liter, filtered, and the filtrate was acidified to *p*H 4 and cooled several hours at 2°. The precipitate was collected on the filter and washed with ice water, and then crystallized (at 5 g./l.) three times from hot 0.1 *N* hydrochloric acid. The material thus obtained had a chemical assay[14] of 66.4%.

4-Aminopteroylserine (VI).—This compound was synthesized from N-(*p*-aminobenzoyl)-serine by the method of Waller, *et al.*,[7] as modified for II above (see Table III) and also by a variation of the procedure of Hultquist and Dreisbach,[9] as indicated above for V. The crude material was heated at 60° with lime in water at a concentration of VI of 1 g./l. The solution was filtered and the filtrate was adjusted to *p*H 10.5–11.0 with aqueous zinc chloride. Insolubles were removed by filtration and the solution was acidified to *p*H 4, and the precipitated material was collected on the filter. It was extracted with 0.1 *N* hydrochloric acid at 80°. The residue was dissolved in dilute sodium hydroxide and reprecipitated with acid at 80°; after cooling to 10° the yellow, partially crystalline product obtained was filtered and dried. It showed a chemical assay[14] of about 70%. It was purified further by repeating the process above and then extracting with 0.1 *N* hychloric acid and reprecipitating three times more.

Anal. Calcd. for $C_{17}H_{18}O_4N_8 \cdot 3H_2O$: C, 45.1; H, 5.35; N, 24.7; H_2O, 11.9. Found: C, 45.3; H, 5.15; N, 24.7; H_2O, 9.9.

The hot 0.1 *N* hydrochloric acid extracts contain additional 4-aminopteroylserine which can be recovered by cooling and reworking as above.

Other Pteroyl- and 4-Aminopteroylamino Acids.—These were prepared by the method of Waller[7] from the N-(*p*-aminobenzoyl)-amino acids. One-half an equivalent of iodine or sodium dichromate was added during the condensation.

Acknowledgment.—We are indebted to Mr. Kenneth H. Collins for technical assistance in this investigation, to Miss Ruth Abbott for the ultraviolet absorption spectra studies, and to Mr. O. Sundberg and co-workers for the microanalyses.

Summary

1. The N-(*p*-nitrobenzoyl) derivatives of β-alanine, ε-aminocaproic acid, diethyl aminomalonate, isoleucine, sarcosine and tryptophan, have been prepared.

2. The N-(*p*-aminobenzoyl) derivatives of the following amino acids have been prepared: alanine, β-alanine, ε-aminocaproic acid, aminomalonic acid, isoleucine, phenylalanine, serine, threonine, tryptophan, and valine.

3. Pteroyl derivatives of alanine, ε-aminocaproic acid, aminomalonic acid, isoleucine, phenylalanine, sarcosine, serine, threonine, tryptophan, valine, β-alanine, cystine and methionine have been prepared as crude reaction products. With the exception of the last three, the corresponding 4-aminopteroylamino acids also have been prepared.

4. Pteroylalanine, pteroyl-β-alanine, pteramidomalonic acid, and 4-aminopteroylserine have been purified.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Fatty Acid Amides. II.[2] Amides as Derivatives for the Identification of Some Long-Chain Unsaturated Fatty Acids

BY DANIEL SWERN, JEANNE M. STUTZMAN AND EDWARD T. ROE

Four techniques are usually employed for the identification of long-chain unsaturated fatty acids. They are (a) rigorous purification of the acid, followed by comparison of its properties with those of the acid with which it is presumed to be identical, (b) cleavage of the acid by any one of several well-known procedures, followed by identification of the fragments, (c) preparation of relatively high melting derivatives involving the ethylenic system, and (d) preparation of derivatives involving the carboxyl group.[3] The relatively high solubility of unsaturated fatty acids in organic solvents, their tendency to form crystalline mixtures of invariant composition, and the need for extremely low temperatures in their isolation and purification render the first technique time-consuming and impractical, and often it does not produce a product of sufficiently high purity, particularly when complex mixtures of fatty acids are employed as the starting material. The second technique is time-consuming, and in addition the severe conditions sometimes required to cleave the chain may cause isomerization. Furthermore, this technique may not give definitive results because of poor yields of cleavage products and the fact that the stereochemical nature of the parent acid cannot be deduced after the molecule is degraded. The third technique, which is the one most widely used, generally involves the formation of brominated or hydroxylated products. Although quantitative

(1) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture. Article not copyrighted.

(2) For the first paper in this series, see THIS JOURNAL, **71**, 2215 (1949).

(3) Shriner and Fuson, "The Systematic Identification of Organic Compounds," 2nd Edition, John Wiley and Sons, Inc., New York, N. Y., 1940; McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1945; Wild, "Characterisation of Organic Compounds," University Press, Cambridge, England, 1947.