[CONTRIBUTION FROM THE MIDWEST RESEARCH INSTITUTE]

Potential Growth Antagonists. I. Hydantoins and Disubstituted Glycines[1,2]

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Received March 21, 1960

Several 2,2-disubstituted glycines were prepared by the hydrolysis of the intermediate hydantoin in either sulfuric acid or barium hydroxide solution. Acid hydrolysis was satisfactory for the preparation of the dialkyl glycines but led to decomposition during the hydrolysis of the aryl substituted glycines. This route to the synthesis of these amino acids is considered superior to that of the Strecker method.

Preliminary anticancer screening of these amino acids containing no *alpha* hydrogen atom has shown them to be inactive, and therefore, unlike their structural analogue, 1-aminocyclopentanecarboxylic acid.

The present paper is concerned with the synthesis of disubstituted glycines of the type $RR'C(NH_2)$-COOH. Compounds of this type were expected to be metabolic antagonists of value in the chemotherapy of cancer.

A number of compounds belonging to this class have already been prepared and shown to possess biological activity. *In vitro* and *in vivo* studies of disubstituted glycine have revealed wide differences between these compounds and the corresponding natural amino acids. 2-Methylalanine appears incapable of being metabolized.[4] 2-Methyl-DL-tryptophan is an antagonist of tryptophan and has shown activity against staphylococcic infections.[5] 3-(3,4-Dihydroxyphenyl)-2-methyl-DL-alanine (α-methyl-DOPA) is a potent inhibitor of mammalian DOPA decarboxylase *in vitro* but is inactive *in vivo*.[6] 2-Methyl-DL-glutamic acid inhibits the decarboxylation of glutamic acid by glutamic decarboxylase.[7] 2-Methyl-DL-methionine is a potent antagonist of methionine and also blocks the action of D-amino acid oxidase on phenylalanine;[7] it is also reported to be active against Newcastle virus disease.[8] 2-Methylalanine, 2-methyl-DL-serine and 2-hydroxymethyl-DL-serine are accumulated in the rat liver after intraperitoneal injection, but they are not degraded.[9] The *alpha* hydrogen of serine appears to be necessary for the reaction with pyridoxal and its subsequent conversion to glycine.[9] *N*-Carbamoyl-2-methyl-DL-glutamic acid did not catalyze the conversion of ornithine to citrulline as did *N*-carbamoyl-DL-glutamic acid.[10] 2-Methyl-DL-serine does not undergo oxidative deamination in the presence of L- or D-amino oxidase.[11] 2-Methyl-DL-valine inhibits penicillin synthesis from lactose, but this inhibition is reversed by valine.[12]

Compounds which inhibit specific metabolic reactions can also be expected to possess selective toxicity and therefore are obvious candidates for trial in cancer chemotherapy. A few members of this group have been screened for their effects upon experimental tumors. 2-Amino-2-methylbutyric acid did not inhibit the growth of mouse Sarcoma-180, Carcinoma-755, or Leukemia-1210.[13] On the other hand, 2-methylalanine, 1-amino-cyclohexanecarboxylic acid, and 1-amino-cyclopentanecarboxylic acid inhibited the development of the Novikoff hepatoma in the rat.[14] The latter compound has also been found to be active on at least one of the mouse tumors mentioned above.[14] 1-Aminocyclohexanecarboxylic acid, 1-amino-1,2,3,4-tetrahydro-1-naphthoic acid, and 2-amino-1,2,3,4-tetrahydro-2-naphthoic acid were inactive in inhibiting the growth of transplanted Walker rat carcinoma; however, 1-aminocyclopentanecarboxylic acid as well as its N- and C-terminal peptides with glycine were very effective in retarding growth in this same system.[15]

Two general methods were considered for the preparation of the disubstituted glycines: the Strecker reaction, *i.e.*, the reaction of a ketone with an alkali cyanide and ammonium chloride to give the amino nitrile followed by hydrolysis to the

(1) This research was supported by Contract No. SA-43-ph-2394 with the Cancer Chemotherapy National Service Center, National Cancer Institute of the National Institutes of Health, Bethesda, Md.

(2) Presented in part at the 136th National Meeting of the American Chemical Society, September 13–18, 1959.

(3) Midwest Research Institute Sabbatical Fellow 1958–59 from Colorado State University, Fort Collins, Colo.

(4) T. R. Riggs and L. M. Walker, *J. Biol. Chem.*, **233**, 132 (1958).

(5) K. Pfister, 3rd and W. J. Leanza, U. S. Patent **2,766,255** (1956); *Chem. Abstr.*, **51**, 6702*i* (1957).

(6) G. A. Stein, H. A. Bronner, and K. Pfister, 3rd, *J. Am. Chem. Soc.*, **77**, 700 (1955).

(7) K. Pfister, 3rd, W. J. Leanza, J. P. Conbere, H. J. Becker, A. R. Matzuk, and E. F. Rogers, *J. Am. Chem. Soc.*, **77**, 697 (1955).

(8) A. R. Matzuk, K. Pfister, 3rd, and E. F. Rogers, U. S. Patent **2,824,132** (1958); *Chem. Abstr.*, **52**, 11114b (1958).

(9) H. N. Christensen, A. J. Aspen, and E. G. Rice, *J. Biol. Chem.*, **220**, 287 (1956).

(10) S. Grisolia and P. P. Cohen, *J. Biol. Chem.*, **204**, 753 (1953).

(11) E. Frieden, L. T. Hau, and K. Dittmer, *J. Biol. Chem.*, **192**, 425 (1951).

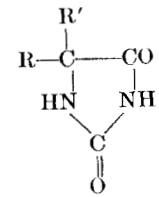
(12) A. L. Demain, *Arch. Biochem. Biophys.*, **64**, 74 (1956).

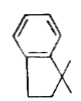
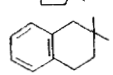
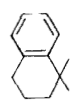
(13)(a) J. Leiter and M. A. Schneiderman, *Cancer Research*, **19**, No. 3, Part II, Cancer Chemotherapy Screening Data II, p. 112 (1959); (b) p. 31 for screening method.

(14) F. Martel and L. Berlinguet, *Can. J. Biochem. and Physiol.*, **37**, 433 (1959).

(15) T. A. Connors, L. A. Elson, and W. C. J. Ross, *Biochem. Pharmacol.*, **1**, 239 (1959).

TABLE I 5,5-DISUBSTITUTED HYDANTOINS

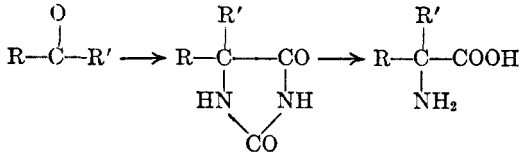


No.	R	R′	Molecular Formula	M.P.	Reported M.P.	Method	Reaction Time, hr.	Yield, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %
1	CH_3	n-C_4H_9	$C_8H_{14}N_2O_2$	113–114	107.5–108.5[a]	A	3	58			16.5			17.2
2	CH_3	n-C_6H_{13}	$C_{10}H_{18}N_2O_2$	106–108.5	107.5–108[a]	A	3	92						
3	CH_3	n-C_7H_{15}	$C_{11}H_{20}N_2O_2$	101–102		A	3	55			13.2			12.8
4	CH_3	n-C_9H_{19}	$C_{13}H_{24}N_2O_2$	110–112	115[b]	A	3	93						
5	CH_3	CH_2=CH—CH_2—CH_2	$C_8H_{12}N_2O_2$	118–119	119.5–120.5[c]	A	3	62	57.1	7.19	16.7	57.9	7.30	16.7
6	CH_3	CH_2=$CH(CH_2)_8$	$C_{14}H_{24}N_2O_2$[c]	88–89		A	3	78			11.1			11.3
7	CH_3	Cyclo C_6H_{11}	$C_{10}H_{16}N_2O_2$	210–211	214.6–215.8[d,e]	A	3	84						
8	CH_3	$C_6H_5CH_2$—CH_2	$C_{12}H_{14}N_2O_2$	176–177	179–180[f]	A	3	87						
9	CH_3	p-F—C_6H_4	$C_{10}H_9FN_2O_2$	205–206	206–207[g]	A	3	55	57.7	4.36	13.5	57.5	4.55	13.5
10	CH_3	2-Thienyl	$C_8H_8N_2O_2S$	136.5–138	138.5–140[h]	B	24	60						
11	C_2H_5	iso-C_3H_7	$C_8H_{14}N_2O_2$	163–165	115–116[h]	A	3	46	56.5	8.29	16.5	56.4	8.23	16.4
12	C_2H_5	p-F—C_6H_4	$C_{11}H_{11}FN_2O_2$	209–210		A	3	67	59.5	4.99	12.6	59.3	5.02	12.4
13	C_6H_5	p-CH_3—C_6H_4	$C_{16}H_{14}N_2O_2$	225–226	229–230[i]	C	24	52						
14	C_6H_5	$C_6H_5CH_2$	$C_{16}H_{14}N_2O_2$	210–211	210–211[j]	A	8	85						
15	C_6H_5	p-Cl—$C_6H_4CH_2$	$C_{16}H_{13}ClN_2O_2$	212–213		C	24	73	63.9	4.36	9.32	63.7	4.58	9.33
16	C_6H_5	$C_6H_5CH_2CH_2$	$C_{17}H_{16}N_2O_2$	195–197	201[k]	A	15	74						
17	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_{17}H_{16}N_2O_2$	320–321	305[j]	A	3	78	72.8	5.75	9.99	72.3	5.98	10.0
	R and R′ Combined													
18			$C_{11}H_{10}N_2O_2$	239–240	240[a]	B	24	69	65.3	4.98	13.9	65.1	4.96	13.7
19			$C_{12}H_{12}N_2O_2$	267–268	268[m]	A	3	79						
20			$C_{12}H_{12}N_2O_2$	241–242.5		A	8	52	66.7	5.59	13.0	66.6	5.73	12.9
21			$C_9H_{14}N_2O_2$	215.5–216.5	215.5–216[a]	A	3	81						

[a] H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 523 (1942). [b] M. Tiffeneau, *et al.*, *Bull. soc. chim. France* **1947**, 445. [c] The ketone, 11-dodecene-2-one, was prepared according to the method of Cason [J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946)]. Semicarbazone m.p. 113–114°; reported m.p. 112–113° [N. Polgar and R. Robinson, *J. Chem. Soc.*, 389 (1945). [d] H. R. Henze, L. M. Long, R. J. Speer, and T. R. Thompson, *J. Am. Chem. Soc.*, **65**, 324 (1943). [e] The ketone, cyclohexyl methyl ketone, was prepared according to the method of Cason [J. Cason, *J. Am. Chem. Soc.*, **68**, 2078 (1946)]. B.p. 180–181°. [f] R. M. Herbst and T. B. Johnson, *J. Am. Chem. Soc.*, **54**, 2467 (1932). [g] J. J. Spurlock, *J. Am. Chem. Soc.*, **75**, 1115 (1953). [h] A compound of this reported structure was prepared from an amino acid and potassium cyanate; however, no analysis was given. [Kuo-Hao Lin, Liang Li, and Yao-Tseng Huang, *Sci. and Technol. China*, **1**, 5 (1948)]. [i] H. R. Henze and A. F. Isbell, *J. Am. Chem. Soc.*, **76**, 4152 (1954). [j] K. H. Slotta, R. Behnisch, and G. Szyska, *Ber.*, **67B**, 1529 (1934). [k] H. R. Henze and L. M. Long, *J. Am. Chem. Soc.*, **63**, 1936 (1941). [m] W. C. J. Ross and T. A. Connors, private communication. [n] G. Quadbeck and E. Röhm, *Arzneimittel-Forsch.*, **6**, 531 (1956). [o] F. J. Marshall, *J. Am. Chem. Soc.*, **78**, 3696 (1957).

amino acid; and the synthesis of an amino acid by the hydrolytic cleavage of a hydantoin. From preliminary experiments it was seen that for the preparation of the dialkyl substituted amino acids, either the Strecker method or the hydantoin method gave comparable yields of the amino acid. The hydantoin method was selected as the preferred route for several reasons. The reactions, in the case of the hydantoin method, proceeded with less decomposition. Even where the reactions were incomplete, the unchanged starting material was easily recovered from the reaction mixture. Furthermore, the hydantoins are readily purified and relatively stable, while the amino nitriles are neither stable nor easily purified. Finally, it was found easier to apply forcing conditions to the preparation and hydrolysis of the hydantoins of hindered ketones, *e.g.*, 4-methylbenzophenone, rather than to use the Strecker reaction.

The hydantoins (Table I) were prepared from the appropriate ketones by the Bucherer-Berg reaction, a method that has been adequately reviewed by Ware[16] and refined by Henze[17] in the last few years. The hydrolysis of the dialkyl hydantoins in 60% sulfuric acid gave good yields of the amino acids. The hydrolyses of the aryl substituted hydantoins were much less successful in acid due to their low solubility in the reaction solutions and the large amount of decomposition which accompanied the reaction. As a result, the the use of barium hydroxide under autoclave conditions was instituted. This method proved satisfactory for the hydrolysis of both the aryl substituted hydantoins and the unsaturated alkyl substituted hydantoins. The preferred reaction sequence is illustrated below and the disubstituted glycines are shown in Table II, where R and R′ = alkyl and aryl. Reaction conditions are more fully described in the experimental section.



The compounds described in Tables I and II have been submitted to the Cancer Chemotherapy National Service Center for screening.[18b] Preliminary results indicate that these compounds are neither capable of producing significant inhibition of the growth of Sarcoma-180 or Carcinoma-755 nor do they increase the survival time of mice bearing Leukemia L-1210. Detailed screening results of these compounds will be published by the National Institutes of Health at a later time.

(16) E. Ware, *Chem. Revs.*, **46**, 403 (1950).

(17)(a) H. R. Henze and R. J. Speer, *J. Am. Chem. Soc.*, **64**, 522 (1942). (b) H. R. Henze and A. F. Isbell, *J. Am. Chem. Soc.*, **76**, 4152 (1954).

EXPERIMENTAL[18]

Preparation of hydantoins. The hydantoins were synthesized from commercially available ketones according to methods described by Henze and co-workers.[17] In cases where the ketones were not available, they were prepared as noted in Table I. The three methods used for the preparation of the hydantoins are illustrated as follows:

Method A.[17a] *5-Ethyl-5-p-fluorophenylhydantoin.* In a three-necked flask equipped with a mercury-seal stirrer, a dropping funnel, and reflux condenser were placed 46 g. (0.33 mole) of 4′-fluoropropiophenone, 100 g. of reagent grade ammonium carbonate, and 550 ml. of 60% ethanol. The mixture was stirred and warmed to 50°, at which time 17 g. (0.35 mole) of sodium cyanide dissolved in 50 ml. of water was added over a period of 5 min. The reaction mixture was then stirred for 3 hr. at temperatures between 56° and 60°. The reflux condenser was then replaced by an air condenser and the temperature raised to 85° for 1 hr. to remove the excess ammonium carbonate. The reaction solution was cooled, acidified to *p*H 6, and chilled to 0° for 24 hr. The precipitate was collected and washed with several portions of cold water. The product was then purified by dissolving it in 300 ml. of 5% aqueous sodium hydroxide solution, the solution filtered, and the filtrate washed with three 50-ml. portions of ether to remove unchanged ketone. The aqueous layer was then cooled and acidified to *p*H 6 and the precipitate collected and recrystallized from 95% ethanol; yield, 44 g., m.p., 209–210.5°.

Anal. Calcd. for $C_{11}H_{11}FN_2O_2$: C, 59.45; H, 4.99; N, 12.61. Found: C, 59.32; H, 5.02; N, 12.44.

Method B.[19] *Spiro[imidazolidine-4,1′-indan]-2,5-dione.* Forty-four grams (0.33 mole) of 1-indanone was mixed with 33 g. (0.5 mole) of potassium cyanide and 114 g. of reagent grade ammonium carbonate. The solids and 350 ml. of 70% ethanol were placed in a stainless steel reaction vessel, sealed, and heated to 110° for 24 hr. The bomb was cooled, the contents removed, filtered and diluted with 100 ml. of water. The reaction solution was then heated to boiling for 15 min. to remove the excess ammonium carbonate, cooled, and acidified to *p*H 6. The resulting precipitate was filtered and recrystallized from 95% ethanol; yield, 46 g., m.p., 239–240°.

Anal. Calcd. for $C_{11}H_{10}N_2O_2$: C, 65.33; H, 4.98; N, 13.86. Found: C, 65.09; H, 4.96; N, 13.68.

Method C.[17b] *5-(p-Chlorobenzyl)-5-phenylhydantoin.* Twenty-three grams (0.10 mole) of 2-(*p*-chlorophenyl)-acetophenone, 7 g. (0.11 mole) of potassium cyanide, 34 g. of reagent grade ammonium carbonate and 250 g. of fused acetamide were intimately mixed and then placed in a stainless steel reaction vessel which was sealed and heated to 110° for 24 hr. After cooling, the contents were removed by washing with 500 ml. of boiling water in several portions. The reaction product was then filtered and washed several times with cold water. The crude hydantoin was decolorized with activated charcoal in hot 95% ethanol, precipitated by cooling, and recrystallized a second time from ethanol; yield, 22 g., m.p., 212–213°.

Anal. Calcd. for $C_{16}H_{13}ClN_2O_2$: C, 63.89; H, 4.36; N, 9.32. Found: C, 63.70; H, 4.57; N, 9.33.

Preparation of amino acids. The hydrolysis of the hydantoins listed in Table I was carried out in both acid and basic solution. Conditions for the preparation and isolation of the amino acids (Table II) are illustrated by the following examples:

Method A. Acid hydrolysis.[20] *2-Amino-2-methylnonanoic*

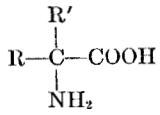
(18) All melting points are uncorrected; analyses were performed by Galbraith Microanalytical Laboratories and Micro-Tech Laboratories.

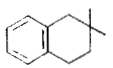
(19) E. Campaigne and H. L. Thomas, *J. Am. Chem. Soc.*, **77**, 5365 (1955).

(20) H. T. Bucherer and W. T. Steiner, *J. prakt. Chem.*, **140**, 291 (1934).

TABLE II

DISUBSTITUTED GLYCINES



No.	R	R′	Molecular Formula	M.P., dec Sealed Tube	Method	Reaction Time, hr.	Yield, %	Calcd. C, %	Calcd. H, %	Calcd. N, %	Found C, %	Found H, %	Found N, %
1	CH_3	n-C_4H_9	$C_7H_{15}NO_2$	308–309	A	72	60			9.63			9.44
2	CH_3	n-C_6H_{13}	$C_9H_{19}NO_2$	280–284	A	72	72			8.08			7.58
3	CH_3	n-C_7H_{15}	$C_{10}H_{21}NO_2$	296–300	A	72	58			7.48			7.33
4	CH_3	n-C_9H_{19}	$C_{12}H_{25}NO_2$	284–286	A	72	66			6.50			6.29
5	CH_3	CH_2=$CHCH_2CH_2$	$C_7H_{13}NO_2$	312–314	B	0.5	87	58.7	9.15	9.78	58.9	8.97	9.86
6	CH_3	CH_2=$CH(CH_2)_8$	$C_{13}H_{25}NO_2$	258–260	B	2.5	81			6.16			6.20
7	CH_3	Cyclo C_6H_{11}	$C_9H_{17}NO_2$	308–309	A	72	57			8.18			8.04
8	CH_3	$C_6H_5CH_2CH_2$	$C_{11}H_{15}NO_2$	287–289	A	72	36			7.25			6.99
9	CH_3	p-F—C_6H_4	$C_9F_{10}FNO_2$	271–272	B	6	69	59.0	5.50	7.65	59.0	5.53	7.53
10	CH_3	2-Thienyl	$C_7H_9NO_2S$	205.5–206.5[a]	B	0.5	77	49.1	5.30	8.18	48.9[a]	5.38	8.14
11	C_2H_5	*iso*-C_3H_7	$C_7H_{15}NO_2$	178–179	A	72	43	57.9	10.4	9.65	57.9	10.4	9.81
12	C_2H_5	p-F—C_6H_4	$C_{10}H_{12}FNO_2$	253–254	B	3	81	60.9	6.14	7.10	60.9	6.15	7.05
13	C_6H_5	p-CH_3—C_6H_4	$C_{15}H_{15}NO_2$	244.5–245.0	C	24	75	74.66	6.27	5.81	74.70	6.32	5.75
14	C_6H_5	$C_6H_5CH_2$	$C_{15}H_{15}NO_2$	268–269	A	72	20	74.7	6.22	5.80	74.6	6.26	5.68
15	C_6H_5	p-Cl—$C_6H_4CH_2$	$C_{15}H_{14}ClNO_2$	263–264	C	24	73	65.34	5.12	5.08	65.45	5.14	5.25
16	C_6H_5	$C_6H_5CH_2CH_2$	$C_{16}H_{17}NO_2$	268–269	B	1.5	18	75.3	6.71	5.49	74.7	6.83	5.48
17	$C_6H_5CH_2$	$C_6H_5CH_2$	$C_{16}H_{17}NO_2$	307–308	B	7	35	75.3	6.71	5.49	75.3	6.86	5.59
18	CH_3	n-C_5H_{11}	$C_8H_{17}NO_2$	318–319	Strecker[b]		44			8.81			8.76
19	CH_3	p-CH_3—C_6H_4	$C_{10}H_{13}NO_2$	279–280	Strecker[b]		29			7.82			8.09
	R and R′ Combined												
20			$C_{10}H_{11}NO_2$	225–227	B	5	82	67.78	6.26	7.91	67.73	6.23	8.01
21			$C_{11}H_{13}NO_2$	301–302	B	6	59	69.0	6.85	7.32	69.1	6.79	7.24
22			$C_{11}H_{13}NO_2$	231–232	B	6	67	69.00	6.85	7.32	68.90	7.00	7.28
23			$C_8H_{15}NO_2$	304–305	A	72	64	61.12	9.62	8.91	61.07	9.73	8.84

[a] This is the melting point of the hydrate. The analysis shown was obtained on a sample dried to constant weight at 150°. [b] R. E. Steiger, *Org. Syntheses*, 24, 9 (1944).

acid. In a three-necked flask fitted with a reflux condenser and nitrogen inlet tube were placed 45 g. (0.02 mole) of 5-heptyl-5-methylhydantoin and 104 g. (0.6 mole) of 60% sulfuric acid. The mixture was then heated at 130° for 72 hr. under a nitrogen atmosphere. The clear, straw-colored solution was then cooled and a precipitate, consisting of amino acid sulfate and unchanged hydantoin, was filtered. The precipitate was dissolved in 300 ml. of hot water, decolorized with activated charcoal, and filtered. The filtrate was cooled and adjusted to *p*H 6 with 10% aqueous ammonia, which precipitated the free amino acid. The mother liquor from the reaction mixture was diluted with 200 ml. of water, decolorized with charcoal, filtered, and the free amino acid precipitated by the addition of 10% aqueous ammonia to *p*H 6. Both crops of amino acid were combined and recrystallized, first, from 50% ethanol and then from acetic acid–water. Finally the product was dried for 24 hr. *in vacuo* at 50°; yield, 23 g., m.p., 296–300° (sealed tube).

Anal. Calcd. for $C_{10}H_{21}NO_2$: N, 7.48. Found: N, 7.33.

Method B. Base hydrolysis.[21] *2-Amino-2-methyl-5-hexenoic acid.* In a stainless steel reaction vessel were placed 30.2 g. (0.18 mole) of 5-(3-butenyl)-5-methylhydantoin, 85 g. (0.27 mole) of barium hydroxide and 485 ml. of water. The bomb was flushed with nitrogen, sealed, and heated to 165° for 30 min. After cooling to room temperature, the alkaline reaction mixture was diluted with 300 ml. of water, then aerated and heated to drive off the ammonia formed in the reaction. The solution was then acidified with concd. sulfuric acid to *p*H 1–2, the barium sulfate filtered, and the *p*H readjusted to 6 with lead carbonate. The solution was filtered free of lead sulfate and then treated with hydrogen sulfide to remove the excess lead ion. The aqueous solution was next heated to boiling, decolorized with charcoal, filtered, and the filtrate concentrated to give three crops of the free amino acid; total yield 22.5 g., m.p., 312–314°. A sample for analysis was recrystallized from 70% ethanol.

Anal. Calcd. for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.91; H, 8.97; N, 9.86.

Several of the amino acids hydrolyzed by this method were insoluble enough in water to be isolated by concentrating the acidic solution to half volume after removing the precipitated barium sulfate and adjusting the *p*H to 6 with concd. ammonium hydroxide. The amino acid was then filtered and washed with several portions of distilled water.

Method C. Base hydrolysis. 2-Phenyl-2-p-tolylglycine. A stainless steel reaction vessel containing 22.6 g. (0.085 mole) of 5-phenyl-5-*p*-tolylhydantoin and 370 ml. of a 20% sodium hydroxide solution was flushed with nitrogen, sealed, and heated to 165° for 24 hr. The cooled reaction mixture was diluted with 1 l. of water and the *p*H adjusted to <1 with concd. hydrochloric acid. The solution was then treated with charcoal, filtered, and the *p*H readjusted to 6 with ammonium hydroxide; yield, 15 g., m.p., 244.5–245° (sealed tube).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.70; H, 6.32; N, 5.75.

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[CONTRIBUTION FROM THE DEPARTMENT OF NUCLEAR MEDICINE AND BIOPHYSICS OF THE MEDICAL CENTER, UNIVERSITY OF CALIFORNIA AT LOS ANGELES, THE CHEMISTRY DEPARTMENT, FRESNO STATE COLLEGE, AND THE CHEMISTRY DEPARTMENT, LONG BEACH COLLEGE]

Behavior of Certain Pyridines, Quinolines, and Isoquinolines with Amino or Hydrazino Substituents Toward *N*-Acylamino Acids Under the Influence of Papain Catalysis

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Received October 12, 1959

3-Aminoquinoline and 3-hydrazinoquinoline have been found to undergo reactions with hippuric acid, carbobenzoxyglycine, and carbobenzoxy-L-alanine in the formation of amide-like products. Also, they both effectively resolve carbobenzoxy-DL-alanine and benzoyl-DL-alanine under papain catalysis. When benzoyl-L-alanine is used alone, however, neither of the amino-containing bases undergoes a papain-catalyzed reaction with this single antipode. A number of aminopyridines, aminoquinolines, 4-aminoisoquinoline, and 2-hydrazinoquinoline failed to react, under papain catalysis, with this same selected group of N-acylamino acids.

Papain catalysis of the formation of peptide-like linkages from N-acyl amino acids and aniline or phenylhydrazine was demonstrated in the original research of Max Bergmann and Heinz Fraenkel-Conrat.[3] Groundwork was thereby laid for a diversity of studies[4] which brought forth much informa-

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