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20. Seishi Takagi and Kyozo Hayashi: Studies on the Synthesis of Amino Acids by the Schmidt Reaction. I. Synthesis of Aliphatic Neutral Amino Acids from Alkylmalonic Acid.

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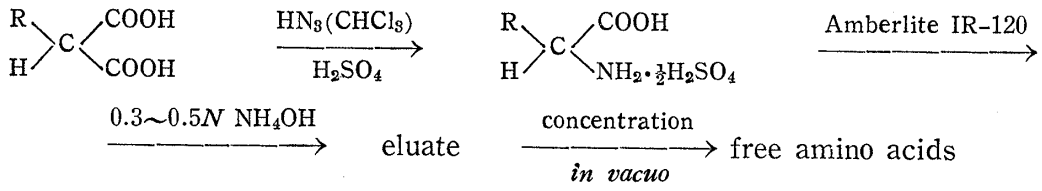
Several methods, including Strecker method, acetamidomalonate method, etc., have been described previously on a general synthesis of amino acids. There were some difficulties in these mehods in the isolation of water-soluble amino acids free from inorganic salts.

Synthesis of amino acids by the Schmidt reaction was examined and by reacting alkylmalonic acid with hydrazoic acid, free amino acids were readily obtained in a pure state after ion-exchange resin treatment.

Adamson[1] obtained glycine with the yield of 46% as ester hydrochloride by the reaction of malonic acid with hydrazoic acid catalyzed by conc. sulfuric acid and esterification of that product. This is the only report concerning the synthesis of aliphatic neutral amino acids from alkylmalonic acid by the Schmidt reaction. This method is rather complicated in the isolation of amino acids from reaction mixture and the hydrochloride formed is very hygroscopic.

In the present series of work, alkylmalonic acid, prepared from alkyl halides and diethyl malonate by the usual method, were reacted with hydrazoic acid in chloroform or benzene solution, and amino acids formed were isolated by either of the two methods (A) or (B) in Chart 1.

Method (A)



Method (B)

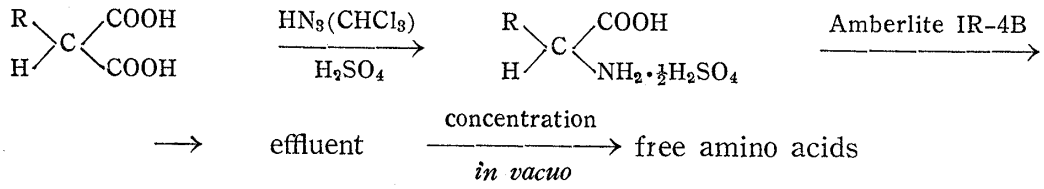


Chart 1.

In Method (A), the sulfuric acid layer is poured into 3~4 volumes of ice water, the solution is neutralized to pH 2~3 with hot conc. barium hydroxide solution, and barium sulfate separated. The reaction mixture containing the amino acids produced is passed through a column of Amberlite IR-120, followed by elution with 0.3~0.5*N* ammonia, and the eluate is concentrated *in vacuo*.

In Method (B), the sulfuric acid layer is neutralized to pH 2~3 as described above, the reaction mixture containing amino acids produced is passed through a column of Amberlite IR-4B, and the effluent is concentrated *in vacuo*.

Method (B) has one less step of procedure. Yield of amino acids is shown in Table I.

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1) D. W. Adamson: J. Chem. Soc., **1939**, 1564.

TABLE I

Amino acids produced	Starting RHC-(COOH)$_2$ R	m.p. (°C)	Yield (%)	Rf value BuOH : HOAc : H_2O (4:1:1)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
Glycine	H	233	49	0.16	white prisms	$C_2H_5O_2N$	32.00	6.71	18.66	32.12	6.95	18.40
2-Amino-butyric acid	C_2H_5	285	89	0.37	brilliant white leaflets	$C_4H_9O_2N$	46.59	8.80	13.58	46.34	8.85	13.46
Alanine	CH_3	295	83	0.29	white needles	$C_3H_7O_2N$	40.44	7.92	15.72	40.29	8.18	15.55
Norvaline	*n*-C_3H_7	291.5	61	0.54	brilliant white leaflets	$C_5H_{11}O_2N$	51.26	9.46	11.96	51.38	9.26	11.90
Valine	*iso*-C_3H_7	298	68	0.50	—do—	$C_5H_{11}O_2N$	51.26	9.46	11.96	51.26	9.45	12.05
Norleucine	*n*-C_4H_9	300	50	0.65	—do—	$C_6H_{13}O_2N$	54.94	9.99	10.68	55.12	10.19	10.82
Isoleucine	*sec*-C_4H_9	275	66	0.62	—do—	$C_6H_{13}O_2N$	54.94	9.99	10.68	54.72	10.00	10.63
Leucine	*iso*-C_4H_9	293	67	0.63	—do—	$C_6H_{13}O_2N$	54.94	9.99	10.68	54.82	9.88	10.96
2-Amino-enanthic acid	*n*-C_5H_{11}	287	54	0.71	—do—	$C_7H_{15}O_2N$	57.90	10.41	9.65	57.92	10.44	9.89
2-Aminoiso-enanthic acid	*iso*-C_5H_{11}	285	59	0.72	—do—	$C_7H_{15}O_2N$	57.90	10.41	9.65	58.14	10.42	9.75
2-Amino-caprylic acid	*n*-C_6H_{13}	263	38	0.77	—do—	$C_8H_{17}O_2N$	60.34	10.76	8.80	60.29	10.83	8.96

From recent reports,[2] it seems that the formation of amino acid from alkylmalonic acid takes place according to the route shown in Chart 2.

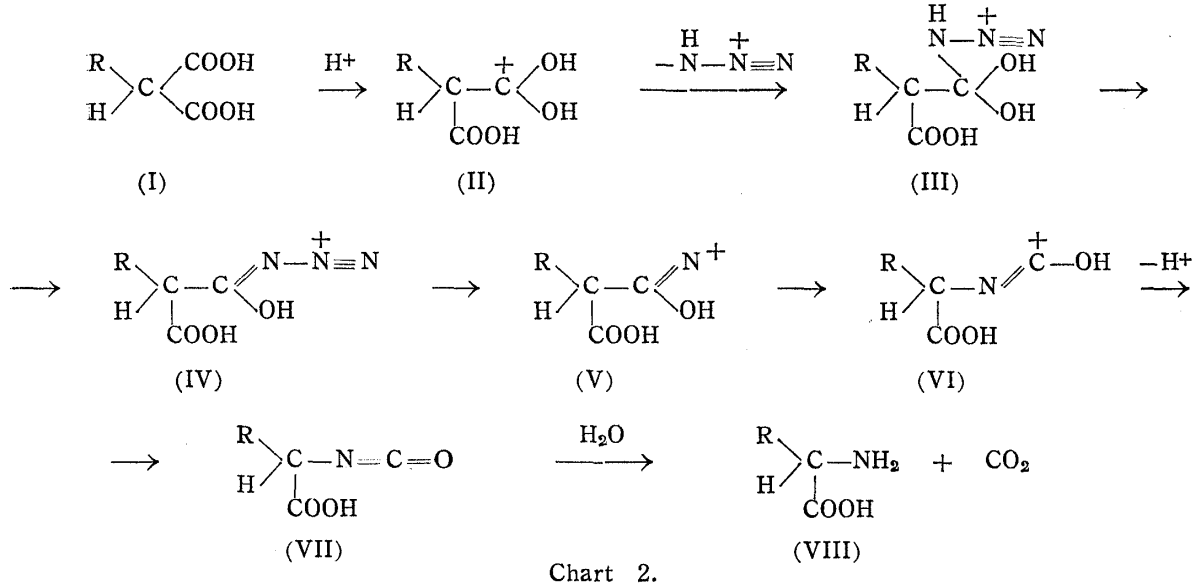

Chart 2.

One of the two carboxyl groups in alkylmalonic acid forms a carbonium cation with a proton from the acid catalyst and (III) is formed by combining with imino-nitrogen of hydrazoic acid, activated by sulfuric acid. (III) is so unstable that nitrogen is easily lost and dehydrated immediately to (V), succeeded by intramolecular rearrangement and liberation of a proton to form the isocyanate (VII), which is readily hydrolyzed to amino acid and carbon dioxide.

About the concentration of sulfuric acid in these reaction, Briggs, *et al.*[3] reported that the yield of aniline from benzoic acid was 85% when using conc. sulfuric acid as a catalyst whereas the yield was only 15% when using 75% sulfuric acid. The same experiments were carried out on ethylmalonic acid, and yields of 89% and 35% were obtained respectively, parallel to those of Briggs' result. As for other catalyst, the use of hydrochloric acid in place of sulfuric acid was tested but the yield was very low. After the end of the reaction, the reaction mixture was concentrated *in vacuo* without being decanted, diluted with

ice water, and unreacted substances were recovered by ether extraction. In these processes, excess hydrazoic acid was separated and thus, it had the advantage of avoiding its toxicity.

The whole procedure of an amino acid synthesis described above is a good method in several points, such as alkylmalonic acid is easily obtainable and amino acid produced is readily isolated in high purity, but there is the problem of strong toxicity of hydrazoic acid.

The authors express their deep gratitude to Prof. T. Suzuki for his kind guidance throughout the course of this work and thanks are due to the members of the microanalytical center of this Institute for the microanalyses.

Experimental

Formation of Amino Acids from Alkylmalonic Acid and Hydrazoic Acid—Alkylmalonic acid (0.01 mole) was dissolved in 2 volumes of 100% H_2SO_4, 10~20 cc. of $CHCl_3$ or benzene was added to it, followed by 0.012 mole of hydrazoic acid (5~10% solution in $CHCl_3$ or benzene) added slowly under vigorous stirring at 50~60°. There occured a violent evolution of gas which ceased after about 2 hrs. The reaction mixture was stirred for 8 hrs. After the reaction completed, $CHCl_3$ or benzene was decanted and H_2SO_4 layer was poured into 2~3 volumes of ice water. After extraction with three 50-cc. portions of ether, the extract was dried with Na_2SO_4, ether was evaporated, and unchanged material was recovered. Residual H_2SO_4 layer was neutralized to pH 2~3 with a hot conc. $Ba(OH)_2$ solution and the precipitated $BaSO_4$ filtered off to obtain a clear solution which was decolorized with activated carbon.

Method (A): This clear solution containing the amino acid produced was passed through a column of Amberlite IR-120 and the column was washed with distilled water until SO_3 ion was no longer found in the effluent. Then the adsorbed amino acid was eluted with 0.3~0.5*N* NH_4OH and the eluate was concentrated *in vacuo*, followed by precipitation with EtOH, filtration, and recrystallization from dil. EtOH.

Method (B): The same clear solution as described above was passed through a column of Amberlite IR-4B and after the effluent was concentrated *in vacuo* free amino acid was obtained by exactly the same procedure as method (A) (for yields see Table I).

Use of conc. HCl as a Catalyst—Alkylmalonic acid (0.01 mole) was dissolved in 10 cc. of conc. HCl under cooling, 10~20 cc. of $CHCl_3$ or benzene was added to it, and 0.012 mole of hydrazoic acid (5~10% solution in $CHCl_3$ or benzene) was added slowly. The reaction mixture was warmed to 40~50° in a water bath and maintained at this temperature for 3 hrs. Reaction mixture was concentrated *in vacuo* to remove excess of HCl, the residue was dissolved in 100 cc. of distilled water, and treated with ion exchange resin in the same manner as described above. Yield of amino acids in the case of methyl-, ethyl- and propylmalonic acid was less than 1%.

Summary

Several amino acids were synthesized from various alkylmalonic acids by reacting with a little excess of hydrazoic acid in chloroform at 50~60°, catalyzed by 100% sulfuric acid. Reaction products were treated with Amberlite IR-120 or Amberlite IR-4B and the expected amino acids were readily obtained in a considerably pure state. In this reaction it seemed that a large alkyl group in alkylmalonic acid tended to lessen the yield of amino acids.

This method is excellent in some points, namely, the starting mateial, alkylmalonic acid, is easily obtainable, the procedure is simple, the yield is high, and there is no fear of inorganic salts contaminated in the products.

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2) R. N. Kellar, P. A. S. Smith: J. Am. Chem. Soc., **66**, 1122(1944); H. Wolfe; "The Schmidt Reaction," Org. Reactions, III (1946); M. S. Newman: "Organic Chemistry Symposium," Boston, Mass., (1947); M. S. Newman, H. Gildenhorn: J. Am. Chem. Soc., **70**, 317 (1948); P. A. S. Smith: *ibid.*, **70**, 320(1948); L. H. Briggs, J. W. Lyttleton: J. Chem. Soc., **1943**, 421.

3) L. H. Briggs, *et al.*: J. Chem. Soc., **1942**, 61.