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21. Seishi Takagi and Kyozo Hayashi: Studies on the Synthesis of Amino Acids by the Schmidt Reaction. II. New Synthetic Method for ω-Amino Acids and Syntheses of DL-2,8-Diaminoöctanoic Acid and DL-2,9-Diaminononanoic Acid.

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Various synthetic methods for ω-amino acids have been reported. For example, for the syntheses of β-alanine, there are succinimide,[1] phthalimide[2], and acrylonitrile method,[3] and for the amino acid which has four or five methylene groups, there is the method[4] in which corresponding lactam is the starting material. As for the synthetic method for 8-aminoöctanoic acid and 9-aminononanoic acid, their oximes are obtained respectively from oxostearic acids[5,6] and octadecanoic 9-acid,[6] which are decomposed by hydrochloric acid. However, these past methods are complicated and general widely applicable method for synthesis of ω-amino acid has not been known so far.

The authors tried the use of the Schmidt reaction for the synthesis of ω-amino acid in an attempt to find a good method which could be applied generally to ω-amino acid. DL-2,8-Diaminoöctanoic acid and DL-2,9-diaminononanoic acid, homologs of lysine, were obtained in a fairly good yield by the process shown in Chart 1, introducing an amino group in the α-position:

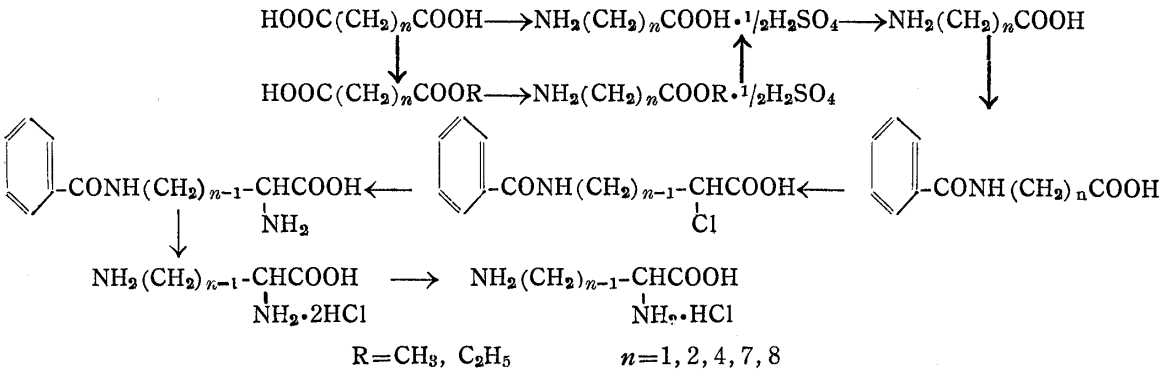

Chart 1.

Equivalent mole of hydrazoic acid was reacted with the dibasic acid, using 100% sulfuric acid as the catalyst and chloroform as the solvent, and the ω-amino acid produced was separated using Amberlite IR-120 as previously reported,[7] in yields as shown in Table I. If more than two moles of hydrazoic acid is used in the Schmidt reaction, the acid should be converted into a diamine, which would be considered a by-product of the synthesis of amino acid, but it was not separated.

It was assumed that a better yield would be achieved if one of the two carboxyls was inactivated and then an excess of hydrazoic acid reacted. The Schmidt reaction was carried out similarly after one of the carboxyls was esterified and ω-amino acid ester formed was

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1) H. T. Clarke, L. D. Behr: Org. Syntheses, Coll. Vol. II, 19(1948).
2) A. Galat: J. Am. Chem. Soc., **67**, 1414(1945).
3) S. R. Buc, *et al.*: *Ibid.*, **67**, 92(1945); J. H. Ford: *Ibid.*, **67**, 876(1945).
4) J. C. Eck: Org. Syntheses, Coll. Vol. II, 28(1943).
5) A. G. Goldsobel: Ber. **27**, 3128(1894).
6) J. Baruch: Ber., **27**, 175(1894).
7) S. Takagi, K. Hayashi: This Bulletin, **7**, 96(1959).

hydrolysed directly without being separated and free amino acids were obtained by the use of ion exchange resin. As expected, a good result was obtained by this method and yields are shown in Table I. In these cases, unreacted starting material was recovered quantitatively.

TABLE I. Yield of ω-Amino Acid

ω-Amino acids	From dibasic acid	From dibasic acid monoester	m.p. (°C)	Rf value (BuOH : HOAc : H_2O = 4 : 1 : 1)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Glycine	49	58	232~236	0.19	white prisms	$C_2H_5O_2N$	32.00	6.71	18.66	32.12	6.95	18.40
β-Alanine	15	79	204	0.33	white plates	$C_3H_7O_2N$	40.44	7.92	15.72	40.53	8.06	15.78
5-Amino-pentanoic acid	16	74	162~163	0.50	white plates	$C_5H_{11}O_2N$	51.26	9.46	11.96	51.49	9.58	12.00
8-Amino-öctanoic acid	20	81	185~186	0.73	white plates	$C_8H_{17}O_2N$	60.34	10.76	8.80	60.34	10.74	8.53
9-Amino-nonanoic acid	28	83	189~191	0.73	white plates	$C_9H_{19}O_2N$	62.39	11.05	8.09	62.70	11.16	8.02

By this method, ω-amino acid ($NH_2(CH_2)_nCOOH$) was obtained in high purity and in high yield from dibasic monoalkyl esters. It was found that a better yield was achieved with increasing number of polymethylene chain, as observed in the preparation of diamines from dibasic acids.[8]

These ω-amino acids obtained here, especially, in which n is four or more, are considered to be the most adequate intermediate for further syntheses of basic amino acids. From this point of view, attempts were made to synthesize according to Galat's method[9] DL-2,8-diaminoöctanoic acid and DL-2,9-diaminononanoic acid, which are regarded as the homologs of lysine, from 8-aminoöctanoic acid and 9-aminononanoic acid, respectively. Generally, basic amino acids are synthesized by the following method. ω-Amino acid is benzoylated, brominated with bromine and red phosphorus, and aminated. On the other hand, Galat reported that chlorination with sulfuryl chloride was more convenient than bromination, because in the case of bromination method, the yield was not constant and the procedure was complicated. Howe, *et al.*[10] reported that the presence of a small quantity of water in bromination allowed the reaction to proceed more smoothly, and usually in high yield.

α-Chloro derivatives were obtained in 90% or higher yield by the use of twice the quantity of sulfuryl chloride with iodine as catalyst, after ω-amino acids of $n=7$ or 8 had been benzoylated by the general method. As the chloro derivative was difficult to crystallize, it was used for next amination without purification. There are generally two methods of amination, the one with excess of ammonia under normal or high pressure, and the other using ammonia with ammonium carbonate. The former method was used in the present experiments. Debenzoylation had to be carried out with 10 times its quantity of 20% hydrochloric acid, refluxing for 8 hours or more in an oil bath. In this case, if the reaction condition was more moderate than this, contamination of unreacted benzoyl derivatives could not be avoided. After the reaction is over, separated benzoic acid is filtered off, and the filtrate is concentrated *in vacuo* to remove hydrochloric acid as much as possible. The residue is recrystallized from acetone and dehydrated ethanol, and dihydrochloride of amino acid is obtained as white crystals. The residue is dissolved in 20~30 volumes of water and the solution is passed through a column of Amberlite IR-120. The amino acid adsorbed is eluted with 0.5~0.6N ammonia, ammonia is removed *in vacuo*, and dil. hydrochloric acid is carefully added to bring its pH to 4~5,

8) D. W. Adamson, J. Kenner: J. Chem. Soc., **1934**, 838.
9) A. Galat: J. Am. Chem. Soc., **69**, 86(1947).
10) E. E. Howe, E. W. Pietrusza: *Ibid.*, **71**, 2581(1949).

concentrated further *in vacuo*, and monohydrochloride of the basic amino acid is easily obtained on addition of ethanol. DL-2,8-Diaminoöctanoic acid and DL-2,9-diaminononanoic acid were obtained as new amino acids, as monohydrochlorides melting at 261~262° and 260~261°, respectively. It is considered that this method is the most useful for the synthesis of ω-amino acid and higher basic amino acids from the following points: (1) Crude dibasic acid monoester can be used as starting materials; (2) higher ω-amino acid, which is the intermediate for the synthesis of basic amino acid, could be synthesized rather easily; and (3) the product is obtained in high purity using ion exchange resin.

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Experimental

Reaction of Hydrazoic Acid with Dibasic Acid—0.01~0.011*M* of hydrazoic acid in $CHCl_3$ was added in small portions during 1.0~1.5 hrs. to the mixture of 0.01*M* of dibasic acid, 5 cc. of conc. H_2SO_4, and 10 cc. of $CHCl_3$ under stirring at 50~60°. Stirring was continued for 3~4 hrs., the reaction mixture was poured on ice, and the aqueous layer was extracted with ether to recover the unreacted starting material. The aqueous layer was adjusted to pH 2~3 with hot saturated $Ba(OH)_2$, $BaSO_4$ precipitated was filtered off, and the filtrate was treated with activated carbon. The solution was passed through a column of Amberlite IR-120, the resin was washed with water until no trace of SO_4^{2-} was found in the effluent, and eluted with 200 cc. of 0.3~0.5*N* NH_4OH. The eluate was concentrated *in vacuo*, EtOH was added to the residue, and separated product was recrystallized from dil. EtOH (for yield and m.p. see Table I).

Reaction of Hydrazoic Acid and Dibasic Acid Monoalkyl Ester—A mixture of 0.01*M* of the dibasic acid monoalkyl ester, 5 cc. of conc. H_2SO_4, and 10 cc. of $CHCl_3$ was kept at 50~60° and 0.02~0.022*M* of hydrazoic acid in $CHCl_3$ was added slowly. The reaction mixture was maintained at this temperature for several hrs. and poured into 10~15 cc. of ice water. The mixture was refluxed for 1.5~2.0 hrs. to effect hydrolysis and the ω-amino acids formed were separated in the same manner as described above (for yield and m.p. see Table I).

8-Benzamidoöctanoic Acid—The crystals obtained by the usual Schotten-Baumann method from 3.3 g. of 8-aminoöctanoic acid, 4.2 g. of BzCl, and 2.4 g. of NaOH were recrystallized from dil. EtOH to white plates, m.p. 87~88°. Yield, 2.7 g. *Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found; C, 68.54; H, 8.29; N, 5.31.

8-Benzamido-2-chloroöctanoic Acid—A mixture of 1.0 g of 8-benzamidoöctanoic acid, 0.02 g. of powdered iodine, and 2.0 cc. of SO_2Cl_2 was heated at 100°, the excess of SO_2Cl_2 was distilled off *in vacuo*, and the residue was washed twice with 2 cc. of water and twice with 2 cc. of hot water. After keeping in desiccator, yellow solid was obtained. Yield, 1.1 g.

DL-8-Benzamido-2-aminoöctanoic Acid—A mixture of 1.1 g. of 8-benzamido-2-chloroöctanoic acid and 20 cc. of 28% NH_4OH was heated for 8 hrs. in a pressurized bottle at 95~100°. After cool, the crystals obtained by vacuum concentration were recrystallized from hot water to a white crystalline powder, m.p. 276~278°. Yield, 0.18 g. *Anal.* Calcd. for $C_{15}H_{22}O_3N_2$: C, 64.72; H, 7.97; N, 10.07. Found: C, 64.64; H, 8.11; N, 9.97.

DL-2,8-Diaminoöctanoic Acid Dihydrochloride—A mixture of DL-8-benzamido-2-aminoöctanoic acid, 6.0 cc. of conc. HCl, and 4.0 cc. of water was refluxed for 8~10 hrs. in an oil bath. After cool, separated benzoic acid was filtered off and the filtrate was concentrated *in vacuo*, water was added to the residue, and the solution was again concentrated. This procedure was repeated several times to remove excess of HCl. The residue was dissolved in EtOH, insoluble substance was filtered off, then acetone was added, and the mixture was kept in a cold place. Colorless crystalline mass was obtained, m.p. 225~228° (from EtOH-acetone). Yield, 0.3 g. *Anal.* Calcd. for $C_8H_{20}O_2N_2Cl_2 \cdot {}^1/_2H_2O$: C, 37.51; H, 8.26; N, 10.93. Found: C, 37.38; H, 8.24; N, 11.08.

DL-2,8-Diaminoöctanoic Acid Monohydrochloride—A mixture of 0.5 g. of DL-8-benzamido-2-aminoöctanoic acid, 6.0 cc. of conc. HCl, and 4.0 cc. of water was refluxed for 8~10 hrs. in an oil bath. After cool, separated benzoic acid was filtered off, the filtrate was concentrated *in vacuo*, and the residue was dissolved in about 30 cc. of water. This solution was treated with activated carbon, the filtrate was passed through a column of Amberlite IR-120, and the column was washed with distilled water until no trace of Cl^- was found in the effluent. The column was eluted with about 200 cc. of 0.5~0.6*N* NH_4OH, the eluate was concentrated, and then carefully neutralized with HCl to pH 4.0~5.0. This was concentrated *in vacuo*, EtOH was added to the residue, and crystals separated were recrystallized from H_2O-EtOH to white needles, m.p. 261~262°. Yield, 0.3 g. *Anal.* Calcd. for $C_8H_{19}O_2N_2Cl$: C, 45.60; H, 9.09; N, 13.30. Found: C, 45.83; H, 8.95; N, 13.06.

9-Benzamidononanoic Acid—Obtained by the same procedure as for 8-benzamidoöctanoic acid from 9-aminononanoic acid (2.6 g.), BzCl (6.3 g.), and NaOH (3.6 g.). White plates (from acetone-petr. ether), m.p. 78~80°. Yield, 2.9 g. *Anal.* Calcd. for $C_{15}H_{23}O_3N$: C, 69.32; H, 8.31; N, 5.25. Found: C, 69.17; H, 8.60; N, 5.24.

9-Benzamido-2-chlorononanoic Acid—Obtained in the same way as for 8-benzamido-2-chloroöctanoic acid from 9-benzamidononanoic acid (1.0 g.), powdered iodine (1.0 g.), and SO_2Cl_2 (2.0 cc.). Yield, 1.05 g.

DL-9-Benzamido-2-aminononanoic Acid—Obtained by the same procedure as for 8-benzamido-2-aminoöctanoic acid from 9-benzamido-2-chlorononanoic acid (1.05 g.) and 28% NH_4OH (25 cc.). White amorphous powder (from hot water), m.p. 225~227°. Yield, 0.78 g. *Anal.* Calcd. for $C_{16}H_{24}O_3N_2$: C, 65.72; H, 8.27; N, 9.58. Found: C, 65.83; H, 8.37; N, 9.71.

DL-2,9-Diaminononanoic Acid Dihydrochloride—Obtained by the same procedure as for DL-2,8-diaminoöctanoic acid dihydrochloride from DL-9-benzamido-2-aminononanoic acid (0.5 g.), conc. HCl (3.0 cc.), and water (2.0 cc.). Colorless powder (from EtOH-acetone), m.p. 220~223°. Yield, 0.31 g. *Anal.* Calcd. for $C_9H_{20}O_2N_2 \cdot 2HCl$: C, 41.36; H, 8.48; N, 10.73. Found: C, 41.56; H, 8.68; N, 10.60.

DL-2,9-Diaminononanoic Acid Monohydrochloride—Obtained by the same procedure as for DL-2,8-diaminoöctanoic acid monohydrochloride from DL-9-benzamido-2-aminononanoic acid (0.5 g.), conc. HCl (3.0 cc.), and water (2.0 cc.). White needles (from dil. EtOH), m.p. 260~261°. Yield, 0.29 g. *Anal.* Calcd. for $C_9H_{20}O_2N_2 \cdot HCl$: C, 48.10; H, 9.42; N, 12.47. Found: C, 48.15, H, 9.63; N, 12.21.

Summary

A new method was found for synthesis of ω-amino acids in a good yield by the Schmidt reaction, reacting basic acids with calculated amount of hydrazoic acid. In this case, the use of monoalkyl ester of dibasic acid as the starting material gave still better yield. In addition, DL-2,8-diaminoöctanoic acid and DL-2,9-diaminononanoic acid were obtained in a high yield as their monohydrochlorides from 8-aminoöctanoic acid and 9-aminononanoic acid, respectively, which were prepared by the above-mentioned reaction.

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