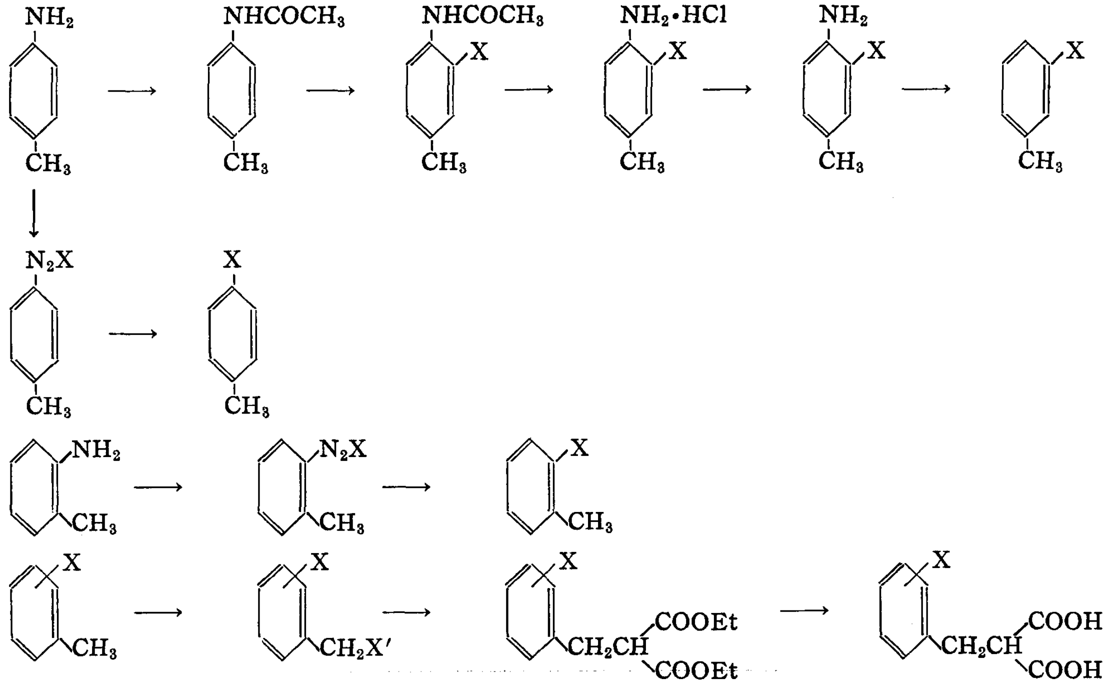
UDC 547.586.2.07

170. **Kyozo Hayashi** : Studies on the Synthesis of Amino Acids by the Schmidt Reaction. V.[1] Synthesis of Phenylalanine Analogs.

(*Pharmaceutical Institute, Medical Faculty, University of Kyoto**)

It has already been reported[1] that amino acids were obtained in a good yield from alkylmalonic acid by the Schmidt reaction. This paper deals with the synthesis of phenylalanine analogs and the effect of the benzene ring and its substituent on the reaction. Briggs, *et al.*[2] have already reported that phenylalanine was obtained in 15% yield when benzylmalonic acid and hydrazoic acid were reacted in chloroform-dioxane using sulfuric acid as a catalyst and the acid layer was neutralized with sodium acetate. However, the yield indicated by Briggs was not obtained and only 2~3% yield was observed in the present experiment.

In regard to the syhthesis of arylmalonic acid, each of the benzylmalonic acids was prepared by the reaction process shown in Chart 1.



X=Cl, Br, I
X′=Br

Chart 1.
Process of Synthesis of Benzylmalonic Acids

In this reaction, bromination in general was carried out under the illumination of ultraviolet ray, but the bromide was obtained in a considerably good yield by reacting in an oil bath under the illumination of a 100-W electric lamp.

Halo- and methyl-phenylmalonic acids were obtained by the procedure indicated in Chart 2 which was used by Levene, *et al.*[3] for the synthesis of phenylmalonic acid.

Halobenzyl bromide was converted into the nitrile which was hydrolyzed with a solution consisting of equal volumes of conc. sulfuric acid, acetic acid, and water, and

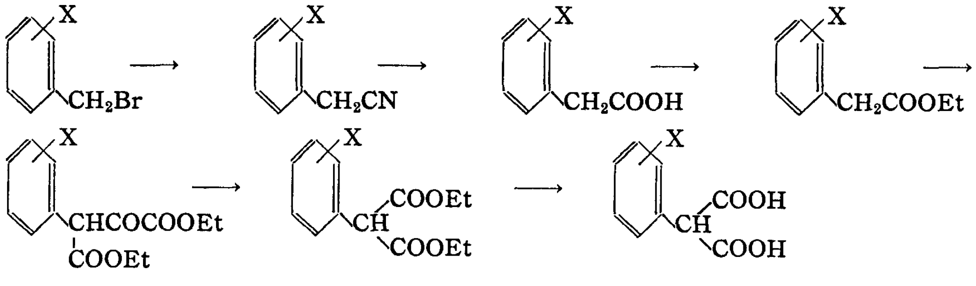
---

* Sakyo-ku, Kyoto (林 恭三).

[1] Part IV. This Bulletin : **7**, 96(1959).

[2] L. H. Briggs, J. W. Lyttleton : J. Chem. Soc., **1942**, 61.

[3] P. A. Levene, G. M. Meyer : Org. Syntheses, **16**, 33(1943).



X=CH_3, Br, Cl

Chart 2. Process of Synthesis of Phenylmalonic Acids

esterified with dehyd. ethanol saturated with dry hydrogen chloride gas followed by condensation with ethyl oxalate, and then decarboxylated.

Thus various kinds of arylmalonic acids obtained were used as the starting material and the Schmidt reaction was carried out under different reaction conditions. The results are shown in Table I.

TABLE I. Discussion of Experimental Conditions

Material (1 mole.)	Temp. (°C)	Time (hrs.)	Catalyst	Solvent	Yield (%)	NH_3 (mol.)
Benzylmalonic acid	45~50	5~6	conc. H_2SO_4	$CHCl_3$	trace	×1.2
Benzylmalonic acid	45~50	5~6	〃	〃	trace	×2.0
Benzylmalonic acid	room temp.	5~6	100% H_2SO_4	〃	0	×1.2
Benzylmalonic acid	0~5	8~10	〃	〃	0	×1.2
Benzylmalonic acid	45~50	5~6	conc. HCl	〃	0	×1.2
Benzylmalonic acid	45~50	5~6	conc. H_2SO_4	Benzene	18	×2.0
Benzylmalonic acid	10~15	8~10	〃	〃	5	×2.0
o-Methylbenzylmalonic acid	45~50	5~6	〃	$CHCl_3$	18	×1.2
o-Methylbenzylmalonic acid	45~50	5~6	〃	Benzene	38	×2.5

As shown in Table I when $CHCl_3$ was used as a solvent, the yield of the expected product was very low, but when benzene was used as a solvent the yield was 15~18%. This is considered to be due to the fact[4] that benzene has an accelerating effect on the decomposition of hydrazoic acid. The quantity of hydrazoic acid has a marked effect on the yield and it is necessary to use it in excess. As a result of the present experiments, the best condition of this reaction was considered to be reaction between benzylmalonic acid and excess of hydrazoic acid in benzene solution, using conc. sulfuric acid as a catalyst, at 45~50°.

Using the best condition, the reactions between various kinds of malonic acids and hydrazoic acid were carried out, and the separation and purification of the amino acid were made using Amberlite IR-120 as described in a previous report.[1] The results are shown in Table II.

Amino acids thus obtained were readily crystallized from 10~20% hydrochloric acid and their hydrochlorides were obtained as white needles. Melting range and yield of amino acids prepared are shown in Table III.

The foregoing experimental results involve some interesting problems for the interpretation of the reaction between various kinds of arylmalonic acid and hydrazoic acid, as follows:

1) In comparison with the yield of aliphatic amino acids from alkylmalonic acids, the yield from arylmalonic acid is markedly low.

2) A substituent in the benzene ring has a strong effect on the reaction. For ex-

---

[4] K. F. Schmidt: Z. Angew. Chem., **36**, 511(1923).

Table II. Amino Acids produced from Malonic Acids

Amino Acid	m.p. (°C)	Yield (%)	Appearance	Formula	Anal. (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
o-chlorophenylalanine	237	37	white plates	$C_9H_{10}O_2NCl$	54.14	5.05	7.02	54.37	5.10	7.27
m-chlorophenylalanine	238	19	〃	〃	54.14	5.05	7.02	53.85	5.25	7.28
p-chlorophenylalanine	229	36	〃	〃	54.14	5.05	7.02	54.02	5.30	6.83
2,4-dichlorophenylalanine	245	22	amorphous powder	$C_9H_9O_2NCl_2$	46.18	3.87	5.99	46.45	3.91	5.82
3,4-dichlorophenylalanine	218	21	〃	〃	46.18	3.87	5.99	46.02	3.88	5.98
o-bromophenylalanine	245	30	white plates	$C_9H_{10}O_2NBr$	44.28	4.13	5.74	44.09	4.15	5.93
m-bromophenylalanine	226	20	〃	〃	44.28	4.13	5.74	44.24	4.09	5.79
p-bromophenylalanine	258	25	〃	〃	44.28	4.13	5.74	44.48	4.23	5.94
o-iodophenylalanine		0								
p-iodophenylalanine		0								
phenylalanine	264	19	white plates	$C_9H_{11}O_2N$	65.44	6.71	8.48	65.17	6.70	8.75
o-methylphenylglycine	221~222	38	〃	〃	65.44	6.71	8.48	65.40	7.01	8.71
phenylglycine	255	46	〃	$C_8H_9O_2N$	63.56	6.00	9.27	63.45	6.29	9.54
m-methylphenylglycine	246~248	50	〃	$C_9H_{11}O_2N$	65.44	6.71	8.48	65.32	6.92	8.71
o-chlorophenylglycine	214~215	27	〃	$C_8H_8O_2NCl$	51.76	4.34	7.55	51.67	4.29	7.72
o-bromophenylglycine	236~238	30	〃	$C_8H_8O_2NBr$	41.76	3.50	6.09	42.04	3.56	5.97
p-nitrophenylalanine	238~240	32	〃	$C_9H_{10}O_4N_2$	51.42	4.80	13.33	51.53	5.01	13.49
4-phenyl-2-aminobutyric acid	293~294	trace	〃	$C_{10}H_{13}O_2N$	67.02	7.31	7.82	67.15	7.45	7.97
p-methylphenylalanine	275~276	trace	〃	〃	67.02	7.31	7.82	66.87	4.32	8.04
cyclohexylglycine	300	56	〃	$C_8H_{15}O_2N$	61.41	9.75	8.91	61.41	9.75	9.16
cyclohexylalanine	320	50	〃	$C_9H_{17}O_2N$	63.13	10.00	8.18	63.07	10.05	8.38
p-methoxyphenylalanine		0								

Table III. Hydrochlorides of Phenylalanine Analogs

Hydrochlorides	m.p. (°C)	Appearance	Formula	Anal. (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
o-chlorophenylalanine	235~237	white needles	$C_9H_{11}O_2NCl_2$	45.78	4.70	5.93	46.08	4.73	5.73
m-chlorophenylalanine	234~236	〃	〃	45.78	4.70	5.93	45.93	4.97	5.86
p-chlorophenylalanine	232~234	〃	〃	45.78	4.70	5.93	45.80	4.79	6.21
3,4-dichlorophenylalanine	248~250	〃	$C_9H_{10}O_2NCl_3$	39.85	3.73	5.18	39.89	3.84	5.41
2,4-dichlorophenylalanine	248	〃	〃	39.95	3.73	5.18	40.10	3.79	5.35
o-bromophenylalanine	248~250	〃	$C_9H_{11}O_2NBrCl$	38.52	3.95	4.99	38.22	4.09	4.81
m-bromophenylalanine	238~240	〃	〃	38.52	3.95	4.99	38.32	4.02	5.02
p-bromophenylalanine	248~249	〃	〃	38.52	3.95	4.99	38.51	4.03	4.98
p-nitrophenylalanine	230~232	〃	$C_9H_{11}O_4N_2Cl$	43.82	4.50	11.36	44.09	4.69	11.45

ample, when the electronegative group is present in benzene ring, the yield becomes greater than in non-substituted benzene, but when a positive group is present, the expected amino acid is scarcely obtained.

3) Yields of amino acids from phenylmalonic acid, benzylmalonic acid, and phenethylmalonic acid were 46%, 18%, and trace, respectively.

The writer expresses grateful thanks to Prof. T. Suzuki and Prof. T. Uno for their kind advices, and thanks are due to the members of the Microanalytical Laboratory of this Institute for the microanalyses.

Experimental

Benzyl Bromides : 2,4-Dichlorobenzyl Bromide—To a refluxing solution of 23.0 g. of 2,4-dichlorotoluene illuminated with a 100-W tungsten lamp, 7.5 cc. of bromine was added at such a rate that the bromine color persisted after all the halogen had been added (ca. 20 min.). When the bromine color almost disappeared, the solution was fractionally distilled *in vacuo*, the product was collected as a fraction of b.p$_8$ 126~133°; yield, 25 g. Because of its strong lachrymatory properties, it was not analyzed but was used immediately in the next step. All the bromides were prepared similarly.

Diethyl 2,4-Dichlorobenzylmalonate—To a solution of 2.3 g. of metallic Na dissolved in 30 cc. of dehyd. EtOH, 16 g. of diethyl malonate and 25 g. of 2,4-dichlorobenzyl bromide dissolved in 25 cc. of dehyd. EtOH was gradually added under cooling in an ice bath. The mixture was heated on a water bath under reflux until the reaction mixture became neutral, EtOH was removed by distillation, and some amount of water was added to the residue so as to dissolve the separated NaBr in the residue. The oily layer was extracted with ether, the extract was dried over Na_2SO_4, and evaporated, the residue was fractionally distilled. The yield and b.p. are shown in Table IV. In this case, diaryl malonate was obtained as a by-product and their constants are also shown in Table IV′. All the malonates were prepared by the same procedure.

TABLE IV. Derivatives of Benzylmalonic Acids and its Diethyl Esters

Ester substituent	b.p. (°C/mm.Hg)	Yield (%)	m.p. (°C)	Appearance	Formula	Anal. (%) Calcd. C	Calcd. H	Found C	Found H
o-chloro-	150~151/2	52	147~147.5	white granules	$C_{10}H_9O_4Cl$	52.53	3.97	52.83	3.99
m-chloro-	193~196/20	43	95~97	〃	〃	52.53	3.97	52.78	4.24
p-chloro-	188~190/20	33	88~93	〃	〃	52.53	3.97	52.59	3.98
o-bromo-	162/2	33	143	〃	$C_{10}H_9O_4Br$	43.98	3.32	44.19	3.42
m-bromo-	155/1.5	36	107~108	〃	〃	43.98	3.32	43.93	3.22
p-bromo-	158~160/2	39	155~156	〃	〃	43.98	3.32	44.24	3.39
o-iodo-	222/38	29	166	〃	$C_{10}H_9O_4I$	37.52	2.83	37.83	2.93
p-iodo-	180/3	26	181	〃	〃	37.52	2.83	37.74	2.87
2,4-dichloro-	158~160/23	59	160	〃	$C_{10}H_8O_4Cl_2$	45.65	3.06	45.67	3.07
3,4-dichloro-	183/35	35	135	〃	〃	45.65	3.06	45.47	3.14
m-methyl-	198/35	42	136	〃	$C_{11}H_{11}O_4$	63.45	5.81	63.47	5.97
p-methyl-	181~184/21	52	158	〃	〃	63.45	5.81	63.27	5.95

Arylmalonic Acids : 2,4-Dichlorobenzylmalonic Acid—19 g. of diethyl 2,4-dichlorobenzylmalonate was hydrolyzed with 25 cc. of 50% KOH according to the general method, neutralized with calculated amount of HCl, extracted with three 30-cc. portions of ether, and the ether was removed by distillation. Crystals obtained were recrystallized from ether and petr. ether. Constants are given in Table IV. All the malonic acids were prepared analogously.

Phenylmalonic Acids : Diethyl *o*-Bromophenylmalonate—11.5 g. of metallic Na was dissolved in 30 cc. of dehyd. EtOH, the solution was cooled to 60°, and 8 g. of ethyl oxalate was added in a rapid stream under vigorous stirring, followed immediately by the addition of 12 g. of ethyl *o*-bromophenylacetate. Stirrer was removed at once, the reaction flask was cooled to room temperature, and 150 cc. of dry ether was added to the reaction mixture. Without isolation of crystals, the next step was followed immediately. Ethyl *o*-bromophenyloxalacetate was liberated from the Na

Table IV′. Diethyl Diarylmalonate obtained as a By-product

Ester Substituent	(m.p.) b.p. (°C/mm Hg)	Yield	Appearance	Formula	Anal. (%) Calcd. C	Calcd. H	Found C	Found H
bis(*m*-chlorobenzyl)-	218/1.5	trace	colorless oil	$C_{21}H_{22}O_4Cl_2$	61.62	5.42	61.89	5.54
bis(3,4-dichlorobenzyl)-	(93)	trace	white granules	$C_{21}H_{20}O_4Cl_4$	52.85	4.19	53.10	4.03
bis(*m*-bromobenzyl)-	265/1.5	trace	colorless oil	$C_{21}H_{22}O_4Br_2$	50.62	4.45	50.39	4.17
bis(*p*-bromobenzyl)-	245/2	trace	〃	〃	50.62	4.45	50.62	4.43

salt with dil. H_2SO_4 (1.8 cc. of conc. H_2SO_4 in 30 cc. of water). The nearly colorless oil was separated and the aqueous layer was extracted with three 50-cc. portions of ether, which was combined with oil. Ether was distilled off and the residual oil, contained in a Claisen flask, was heated under a pressure of about 18 mm. Hg in an oil bath. The temperature of the bath was raised gradually to 180~185° and kept until the evolution of CO was complete. At the end of this reaction (5~6 hr.), the oil which has distilled was returned to the flask and ethyl *o*-bromophenylmalonate was distilled *in vacuo*. The yield and b.p. are shown in Table V. All other phenylmalonic acid esters were prepared analogously.

Table V. Derivatives of Phenylmalonic Acid Analogs and their Diethyl Esters

Ester acid	b.p. (°C/mm Hg)	Yield (%)	m.p. (°C)	Appearance	Formula	Anal. (%) Calcd. C	Calcd. H	Found C	Found H
o-methylphenylmalonic acid	165~171/15	62	157	white granules	$C_{10}H_{10}O_4$	61.85	5.19	61.68	5.09
m-methylphenylmalonic acid	148~151/3	59	137~138	〃	〃	61.85	5.19	61.60	5.29
o-bromophenylmalonic acid	158~160/3	71	133~136	〃	$C_9H_7O_4Br$	41.72	2.73	41.84	2.95

Phenylmalonic Acids: *o*-Bromophenylmalonic Acid—It was obtained in the same manner as described above from 10 g. of ethyl *o*-bromophenylmalonate and 16 cc. of 50% KOH. White granules from a mixture of ether and petr. ether. Results are shown in Table V. All other malonic acids were prepared analogously.

Reaction between Hydrazoic Acid and Arylmalonic Acid: DL-2,4-Dichlorophenylalanine—A mixture of 2,4-dichlorobenzylmalonic acid (2.3 g.), conc. H_2SO_4 (7 cc.), and benzene (10 cc.) was warmed on a water bath at 45~50° and hydrazoic acid in benzene (10.2%) (5.2 cc.) was slowly added with vigorous stirring. After the addition of hydrazoic acid, the reaction was continued for further 3 hrs. Succeeding procedure was the same as in the previous report. White amorphous powder (from hot water). All other amino acids were prepared analogously.

Hydrochlorides: DL-2,4-Dichlorophenylalanine Hydrochloride—It was easily obtained by recrystallization from 20% HCl. The yield and m.p. are shown in Table III. All other hydrochlorides were prepared analogously.

Summary

It has previously been reported that aliphatic amino acid was obtained from alkylmalonic acid using the Schmidt reaction, in a good yield. In this report the synthesis of more than twenty kinds of phenylalanine analogs from arylmalonic acid is described and furthermore, the effect of the benzene ring and its substituents on the reaction was examined, and some new information were obtained.

1) When the group of malonic acid combines directly with the benzene ring, the yield was considerably good.

2) In the case of benzylmalonic acids, when the electronegative group exists in the benzene ring, the expected amino acid was obtained, though in a low yield, but in the case with the positive group in the benzene ring, the expected amino acid was scarcely obtained.

3) From benzylmalonic acid the yield of amino acid was 18%, but from cyclohexylethylmalonic acid, the yield of cyclohexylalanine was 50%.

(Received March 13, 1959)