1250 cm^{-1} (C–O); NMR ($CDCl_3$, Me_4Si) δ 3.83 (s, OCH_3, 6 H), 6.95 (d, J = 9 Hz, arom, 4 H), 7.50 (d, J = 9 Hz, arom, 4 H).

In the case of less soluble biphenyls in ether such as 4,4′-dicyano- or 4,4′-diacetylbiphenyl, chloroform was used for extraction. The reaction mixture was poured into chloroform (150 mL) and washed with 3% HCl solution followed by water (100 mL).

4,4′-Dicyanobiphenyl: mp 236–237 °C (sublimation) (lit.[19] mp 237–238 °C); IR (KBr) 2220 cm^{-1} (C≡N); NMR ($CDCl_3$, Me_4Si) δ 7.69 (d, J = 9 Hz, arom, 4 H), 4.82 (d, J = 9 Hz, arom, 4 H).

4,4′-Diacetylbiphenyl: mp 190–191 °C (glyme) (lit.[20] mp 192–193 °C); IR (KBr) 1675 cm^{-1} (C=O); NMR ($CDCl_3$, Me_4Si) δ 2.60 (s, CH_3CO, 6 H), 7.70 (d, J = 9 Hz, arom, 4 H), 8.05 (d, J = 9 Hz, arom, 4 H).

Trapping of Bis(pentafluorophenyl)nickel(II) Species with Triphenylphosphine. Activated nickel was prepared by stirring a mixture of nickel iodide (2.54 g, 8.14 mmol), lithium (0.130 g, 18.7 mmol), and naphthalene (0.104 g, 0.81 mmol) at room temperature for 12 h. To the nickel powder was added iodopentafluorobenzene (1.85 g, 6.29 mmol), and the mixture was stirred for 24 h at the same temperature. To the formed reddish brown reaction mixture was added triphenylphosphine (4.27 g, 16.28 mmol), and this was stirred overnight at room temperature. The glyme was removed under reduced pressure, the residue was dissolved in benzene (30 mL), and the solution was filtered under argon. The benzene solution was concentrated to 3 mL, and methanol (20 mL) was added. The yellow powder which precipitated was separated by filteration. Recrystallization from benzene–methanol gave the yellow crystalline solid bis(triphenylphosphine)bis(pentafluorophenyl)nickel(II): 1.31 g (45%); mp 203–204 °C dec (lit.[21] mp 201–204 °C dec); IR spectrum is consistent with the reported values.[21]

Trapping of (Pentafluorophenyl)nickel(II) Iodide Species with Triethylphosphine. To nickel powder in glyme (30 mL) prepared from nickel iodide (3.95 g, 12.7 mmol) in a similar manner was added triethylphosphine (2.99 g, 25.3 mmol) at room temperature. After the mixture was stirred 1 h, iodopentafluorobenzene (3.01 g, 10.3 mmol) was added and the mixture stirred at room temperature for 24 h. The reaction mixture was evaporated under reduced pressure, benzene (20 mL) was added to the residue, and the mixture was filtered under argon. The filtrate was evaporated, and the residue was recrystallized from methanol to give the brown crystalline solid bis(triethylphosphine)(pentafluorophenyl)nickel(II) iodide: 0.91 g (15%); mp 149–149.5 °C (lit.[21] mp 151–152 °C). Anal. Calcd for $C_{18}H_{30}F_5INiP_2$: C, 37.10; H, 5.19. Found: C, 36.96% H, 5.17.

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Registry No. C_6H_5I, 591-50-4; 4-$CH_3OC_6H_4I$, 696-62-8; 4-ClC_6H_4I, 637-87-6; 4-NCC_6H_4I, 3058-39-7; C_6F_5I, 827-15-6; 4-ClC_6H_4Br, 106-39-8; 4-$CH_3COC_6H_4Br$, 99-90-1; 4-NCC_6H_4Br, 623-00-7; C_6F_5Br, 344-04-7; 2-$CH_3OC_6H_4I$, 529-28-2; 2-$O_2NC_6H_4I$, 609-73-4; 4-$CH_3OC_6H_4Br$, 104-92-7; nickel, 7440-02-0; bis(triphenylphosphine)bis(pentafluorophenyl)nickel(II), 14832-18-9; bis(triethylphosphine)(pentafluorophenyl)nickel(II) iodide, 13978-69-3.

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Method for the Racemization of Optically Active Amino Acids

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A practical method for the racemization of optically active amino acids has been developed. A wide variety of optically active α-amino acids, including neutral amino acids, acidic amino acids, basic amino acids, and imino acids, could be racemized by heating in a medium of acetic acid at 80–100 °C for 1 h in the presence of 0.05 molar equiv of an aliphatic or an aromatic aldehyde. The factors influencing the racemization were investigated. Phenylglycine, (p-hydroxyphenyl)glycine, and serine could be racemized without complete dissolution of the optically active isomers. Thus, isolation of the racemic modification was easily achieved by simple filtration of the racemic modification suspended in the reaction mixture. The mechanism of the racemization is discussed.

In order to improve the industrial production of optically active amino acids, we have been studying optical resolution of DL-amino acids by preferential crystallization procedures. Since one enantiomer of the racemic modification has economical use, it is desirable to racemize the unwanted enantiomer obtained by optical resolution to recycle it for the resolution process.

Various methods for racemization of optically active amino acids are known. For example, optically active amino acids can be racemized (i) by heating with water in the presence of strong base or strong acid,[1] (ii) by heating with water in the absence of strong base or strong acid in a sealed vessel at 150–250 °C,[2] (iii) by heating with water in the presence of an aldehyde and a metal ion under neutral or weakly alkaline conditions,[3] (iv) by heating with water in the presence of pyridoxal or pyridoxal analogues, including the so-called resin catalyst, and metal ion,[4,5] or (v) by heating with a lower aliphatic acid such as acetic

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Table I. Racemization of Various Amino Acids in Acetic Acid at 100 °C for 1 h

amino acid	racemization, % without salicylaldehyde	racemization, % with salicylaldehyde
L-alanine	13	100
L-arginine	9	100
L-arginine hydrochloride	11	100
L-aspartic acid[a]	4	6
L-glutamic acid[a]	14 (51)[b]	36 (81)[b]
L-histidine hydrochloride	11	100
L-isoleucine[c]	4	93
L-leucine	23	100
L-lysine	9	100
L-lysine hydrochloride[a]	9	67
L-methionine	24	100
L-phenylalanine	35	100
L-proline[d]	3	91
L-serine[e]	1	81
L-tryptophan[e]	0	6
L-tyrosine[a]	0	39
L-valine	4	87

[a] Acetic acid containing 5% water used. [b] Numbers in parentheses indicate the results when the racemization was carried out for 2 h by using acetic acid containing 20% water. [c] The epimerization occurred, and a mixture of L-isoleucine and D-alloisoleucine was obtained. [d] The racemization was carried out by using 0.6 mL of acetic acid. [e] Acetic acid containing 5% water was used, and the reaction was carried out at 80 °C. Some decomposition took place.

acid.[6,7] On economic grounds, however, these methods are still unsatisfactory since some decomposition of the amino acids often occurs at high temperature or the rate of racemization frequently is not practical. Generally, free amino acids are difficult to racemize.

This work was undertaken to develop a simple and economical method for the racemization of optically active amino acids. As can be seen from Table I, racemization of a wide variety of optically active α-amino acids, including neutral amino acids, acidic amino acids, basic amino acids, and imino acids, was found to be greatly accelerated in acetic acid solution in the presence of catalytic amounts of salicylaldehyde. Racemization occurred under mild conditions at a temperature of 80–100 °C. Except for some discoloration in the case of serine and tryptophan, no significant decomposition was observed. As L-aspartic acid, L-glutamic acid, and L-tyrosine were hardly soluble even in acetic acid solution containing 20% or 5% water, the reaction was carried out under heterogeneous conditions. The degree of racemization, however, was lower than that of the other amino acids. Hence, it seems that racemization occurred only in the liquid phase, and the insoluble part of the L isomer in the reaction mixture could not dissolve successively in the reaction mixture saturated with the DL form. This is supported experimentally by the following facts: (i) the precipitates separated from the final reaction mixture were almost optically pure L isomer; (ii) under the conditions of racemization, DL-aspartic acid and DL-glutamic acid crystallized as a racemic mixture but not as a racemic compound, and their optically active isomers were insoluble in a saturated solution of their racemic mixture.

The effect of varying the aldehyde on the racemization is shown in Table II. This shows that various aliphatic

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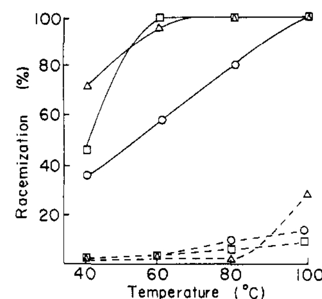


Figure 1. Effect of temperature on racemization of L-amino acids: O, L-alanine; □, L-lysine; △, L-methionine; —, with salicylaldehyde; ---, without salicylaldehyde.

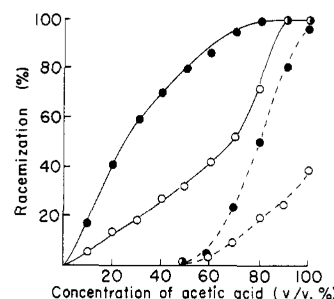
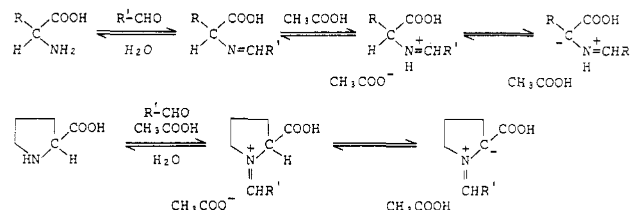


Figure 2. Effect of water content of acetic acid on racemization of L-phenylalanine: O, 1 h; ●, 3 h; —, with salicylaldehyde; ---, without salicylaldehyde.

Scheme I



or aromatic aldehydes can serve as catalysts in place of salicylaldehyde. The effect of varying the amount of aldehyde is shown in Table III. To complete the racemization of L-alanine in acetic acid within 1 h at 100 °C, it is sufficient to use only 0.01 mol of salicylaldehyde/mol of the amino acid. The rate of racemization was also markedly accelerated by increasing the reaction temperature, as shown in Figure 1. L-Lysine and L-methionine were completely racemized even at 60 °C for 1 h without substantial decomposition. Racemization also proceeded when formic or propionic acid was used instead of acetic acid as shown in Table IV, although racemization in acetic acid was most rapid. Racemization may progress by way of initial protonation of the imine, followed by proton abstraction from the α-carbon atom by acetate anion (Scheme I). The racemization rate seems to be dependent on the overall reaction rate of the two steps. From the dissociation constants of the aliphatic acids, the order of protonation should be formic acid > acetic acid > propionic acid while the order of proton abstraction is propionic acid > acetic acid > formic acid. Thus, the overall reaction rate may be largest in acetic acid. When L-phenylalanine was racemized in the presence of salicylaldehyde, the extent of racemization decreased sharply with an increase in the water content of acetic acid (Figure 2). The imine formation from amino acids and an aldehyde, the first step in Scheme I, might be inhibited by the presence of water.

Traditional racemization procedures using an aldehyde also employed a metal ion which forms a chelate compound

Table II. Effect of Kinds of Aldehyde in Racemization Reactions

aldehyde	reaction temp, °C	racemization, % L-Ala	L-Met	L-Phe	L-Pro
none	80	7	0	35	0
	100	13	24	35	3
formaldehyde	100	83	95	100	63
acetaldehyde	100	97	100	100	98
propionaldehyde	100	78	100	100[a]	87
n-butyraldehyde	80	97	95[a]	100[a]	99
n-heptylaldehyde	80	100	100[b]	100[b]	100
acrolein	100	76	100	100[b]	100
benzaldehyde	100	72	100	100	72
salicylaldehyde	80	100	100	100	91
p-hydroxybenzaldehyde	100	75	100	100	48
p-anisaldehyde	80	80	100	100	56
o-nitrobenzaldehyde	80	100[a]	100[a]	100	34
5-nitrosalicylaldehyde	80	100	100	100	91
furfural	100	100[b]	100[b]	100[b]	100[b]

[a] A ninhydrin-positive spot of degradation products was slightly observed on TLC of the reaction mixture. [b] Considerable decomposition was detected by thin-layer chromatography of the reaction mixture.

Table III. Effect of Molar Ratio of Salicylaldehyde to L-Alanine and L-Methionine on Their Racemization[a]

molar ratio	racemization, % L-Ala	L-Met
0	13	24
0.001	46	44
0.005	87	78
0.01	100	95
0.05	100	100
0.1	100	100

[a] The reaction was carried out at 100 °C for 1 h.

Table IV. Comparison of Kinds of Solvent in the Racemization Reaction

aliphatic acid	racemization,[a] % L-Ala	L-Lys	L-Met	L-Phe
formic acid	81	43[b]	49	100
	(53)	(19)[b]	(18)	(95)
propionic acid	9[c]	99[b]	96[b]	100[b]
	(2)[c]	(15)[b]	(19)[b]	(100)[b]
acetic acid	100	100	100	100
	(13)	(9)	(24)	(35)

[a] Numbers in parentheses indicate the results when the racemization was carried out without salicylaldehyde. [b] A ninhydrin-positive spot of degradation products was slightly observed on TLC of the reaction mixture. [c] Because of low solubility, the reaction was carried out under heterogeneous conditions.

with the initially formed Schiff base. Therefore, the reaction was carried out under neutral or weakly alkaline conditions. In the method developed by us, racemization of α-amino acids, including that of proline, is carried out under acidic conditions without metal ions. There is also no restriction on the type of aldehyde which can be used. Roughly speaking, there is no great difference in their catalytic ability to induce racemization. Thus, aldehydes are not restricted to pyridoxal analogues or ortho-substituted benzaldehyde derivatives. Therefore, the mode of action of the aldehyde must be different from that of the previous methods. Moreover, as shown in Table V, the racemization efficiency of the present method was superior to the previous methods or other known methods which use acetic acid without a catalyst. As a practical example, L-alanine, L-lysine, L-methionine, L-phenylalanine, L-proline, L-phenylglycine, L-(*p*-hydroxyphenyl)glycine, and L-serine were racemized by the present method, and the respective racemic amino acids were separated and analyzed. The results are shown in Table VI. The racemized DL-amino acids were obtained in high yield (85–96%) and in such high purity that no byproduct was detected by thin-layer chromatography. Phenylglycine, (*p*-hydroxyphenyl)glycine, and serine were completely racemized even in systems in which large amounts of the amino acids were insoluble. This may be explained as follows. Only dissolved material can be racemized by our method. However, in contrast with the case of aspartic acid or glutamic acid,

Table V. Racemization of Amino Acids under Various Conditions

media	catalyst[a]	temp, °C	racemization, % L-Ala	L-Lys[b]	L-Met	L-Phe	L-Pro
AcOH	none	60	0	0	0	25	0
	SA	60	55	100	97	86	3
	SA, Cu^{2+}	60	38	68	39	42	0
AcOH	none	80	0	0	0	35	0 (3)[c]
	SA	80	72	100	100	100	21 (91)[c]
	SA, Cu^{2+}	80	98	97	100	100	0
H_2O buffered at pH 4[d]	none	100	0	0	0	0	0
	SA	100	0	0	0	0	0
	SA, Cu^{2+}	100	0	0	0	0	0
H_2O buffered at pH 10[e]	none	100	0	0	0	0	0
	SA	100	4	0	0	0	0
	SA, Cu^{2+}	100	31	58	37	27	0

[a] Salicylaldehyde (SA; 0.2 molar equiv) and 0.1 molar equiv of $CuCl_2$ (Cu^{2+}) were used. [b] L-Lysine base was used in a acetic acid solution, and L-lysine hydrochloride was used in a buffered aqueous solution. [c] Numbers in parentheses indicate the results when the racemization was carried out at 100 °C by using 0.6 mL of acetic acid. [d] 1 M CH_3COONa/HCl. [e] 0.2 M $NaCO_3$/$NaHCO_3$.

Table VI. Preparation of DL-Amino Acids by Racemization

compd	composition[i]		reaction		separated crystals[b]			
	AcOH, mL	SA,[a] mL	temp, °C	time, h	yield, g	yield, %	$[\alpha]_D$	optical purity,[c] %
alanine	180	0.35	100	1	5.74	96	0[d]	0
lysine	180	0.22	100	1	6.64[e]	89[e]	0[d]	0
methionine	180	0.21	100	1	5.62	94	0[d]	0
phenylalanine	180	0.19	100	1	5.62	94	0[f]	0
proline	36	0.28	100	1	5.10	85	−8.5[f]	9.9
phenylglycine	20[g]	0.20	100	2	5.36	89	+1.6[h]	1.0
(*p*-hydroxyphenyl)glycine	20[g]	0.20	100	2	5.58	93	+3.3[h]	2.1
serine	20[g]	0.10	80	5	5.14	86	0[h]	0

[a] Salicylaldehyde. [b] The byproduct was not detected by thin-layer chromatography. [c] Based on the values in the literature: L-Ala, $[\alpha]^{25}_D$ +14.6° (*c* 2, 5 N HCl); L-Lys·HCl, $[\alpha]^{25}_D$ +20.8° (*c* 2, 5 N HCl); L-Met, $[\alpha]^{25}_D$ +23.2° (*c* 2, 5 N HCl); L-Phe, $[\alpha]^{25}_D$ −34.5° (*c* 1, H_2O); L-Pro, $[\alpha]^{25}_D$ −85.5° (*c* 1, H_2O); L-PhGly, $[\alpha]^{25}_D$ + 158.0° (*c* 1, 1 N HCl); L-*p*-(OH)PhGly, $[\alpha]^{25}_D$ +158.4° (*c* 1, 1 N HCl); L-Ser, $[\alpha]^{25}_D$ +15.0° (*c* 1, 1 N HCl). [d] *c* = 2 in 5 N HCl. [e] Lysine monohydrochloride. [f] *c* = 1 in H_2O. [g] AcOH/H_2O, 95/5 (v/v). [h] *c* = 1 in 1 N HCl. [i] A 6-g amount of the L form of the compound was used throughout.

DL-phenylglycine, DL-(*p*-hydroxyphenyl)glycine, and DL-serine crystallized as a racemic compound under the racemization conditions, and their optically active isomers could be dissolved into a saturated solution of the respective racemic compounds. Therefore, racemization of the optically active isomer of these amino acids was accomplished even in a heterogeneous system by repeating the following processes: dissolution of the optically active isomer into a saturated solution of the racemized amino acids, racemization of the dissolved optically active isomer, and deposition of the racemized amino acids from the saturated solution. Thus, isolation of these racemic modifications could be easily achieved by simple filtration.

The method presented here may provide a simple and practical way to produce racemic amino acids from optically active amino acids.

Experimental Section

Materials and Methods. Analytical standard grade amino acids manufactured by our company, Tanabe Seiyaku Co., Ltd., were used. All aldehydes were obtained from Tokyo Kasei Kogyo Co., Ltd. These were used without further purification. Both the amino acid and aldehyde were dissolved in acetic acid at suitable concentrations. Unless otherwise noted, the racemization was carried out as follows. A mixture of L-amino acids (1.5 mmol), aldehydes (0.3 mmol), and acetic acid (6.0 mL) was heated in a sealed tube in a water bath at 100 °C. The concentrations of amino acids and aldehydes and the reaction temperature were varied according to each experimental design.

Decomposition of amino acids was checked by thin-layer chromatography (solvent system: *n*-butanol–acetic acid–water, 4:1:1 v/v/v) by using the ascending technique on a Merck No. 60 F_{254} plate. An accurate quantitative determination of amino acids was made by using a Hitachi KLA-3B amino acid analyzer (resin, Hitachi Custom Resin; eluting buffer, citrate buffer [pH 3.25]; temperature, 55 °C). If there was no apparent decomposition, the extents of racemization were obtained by comparing the optical rotation as follows. A 3-mL portion of the reaction mixture at each reaction time was diluted with 1 N hydrochloric acid (5 mL). Then, the optical rotation was measured with a Perkin-Elmer 141 automatic polarimeter. The racemization degree was calculated as follows:

$$100 \times \frac{\text{initial optical rotation} - \text{final optical rotation}}{\text{initial optical rotation}}$$

In the preparations of DL-amino acids, the racemization of proline, phenylglycine, (*p*-hydroxyphenyl)glycine, and serine was carried out at an extremely high concentration of amino acids, sometimes in a heterogeneous system in which large amounts of the amino acids were insoluble. Other amino acids were racemized under the standard conditions. After the reaction, the crystalline amino acids were isolated and analyzed in the usual way described above.

Racemization in Acetic Acid in the Presence of Salicylaldehyde. The racemization of 15 L-amino acids was carried out by heating at 100 °C for 1 h in glacial acetic acid in the presence of 0.2 molar equiv of salicylaldehyde. The results are shown in Table I. For comparison, the results of the racemization reactions without salicylaldehyde are also shown in Table I.

Effect of the Kind of Aldehyde Present. The effect of the kind of aldehyde on the racemization of L-alanine, L-methionine, L-phenylalanine, and L-proline was examined at 80 or 100 °C for 1 h in the presence of 0.2 molar equiv of various aldehydes. The results are shown in Table II. Although furfural was apparently effective, considerable decomposition was detected by thin-layer chromatography of the reaction mixture.

Preparation of DL-Amino Acids by Racemization. In the case of L-alanine, L-lysine, L-methionine, L-phenylalanine, and L-proline, an L-amino acid (6 g) was dissolved in glacial acetic acid (32 mL for L-Pro, 180 mL for other amino acids) containing 0.05 molar equiv of salicylaldehyde (0.19–0.35 mL) and was heated at 100 °C for 1 h under stirring. After the reaction, the mixture was concentrated in vacuo to dryness. The residue was dissolved in water, treated with active charcoal, and concentrated again to dryness. To the residue was added 40 mL of methanol. In the case of lysine, 3.6 mL of concentrated hydrochloric acid was further added. The crystalline precipitates were collected to give the corresponding DL-amino acids.

In the cases of L-phenylglycine, L-(*p*-hydroxyphenyl)glycine, and L-serine, the racemization was carried out at an extremely high content in a heterogeneous system in which amino acids were mostly insoluble. A suspension of an L-amino acid (6 g) in aqueous acetic acid (water/AcOH, 5/95 v/v, 20 mL) containing salicylaldehyde (0.2 mL, or 0.1 mL for L-Ser) was heated at 100 °C (or 80 °C for L-Ser) for 2 h (or 5 h for L-Ser) under stirring. After the reaction, the mixture was cooled in an ice bath. The crystalline precipitates were filtered and washed with methanol. The conditions employed and the results thus obtained are shown in Table VI.

Registry No. L-Alanine, 56-41-7; L-arginine, 74-79-3; L-arginine hydrochloride, 1119-34-2; L-aspartic acid, 56-84-8; L-glutamic acid, 56-86-0; L-histidine hydrochloride, 645-35-2; L-isoleucine, 73-32-5; L-leucine, 61-90-5; L-lysine, 56-87-1; L-lysine hydrochloride, 657-27-2; L-methionine, 63-68-3; L-phenylalanine, 63-91-2; L-proline, 147-85-3; L-serine, 56-45-1; L-tryptophan, 73-22-3; L-tyrosine, 60-18-4; L-valine, 72-18-4; salicylaldehyde, 90-02-8; formaldehyde, 50-00-0; acetaldehyde, 75-07-0; propionaldehyde, 123-38-6; butyraldehyde, 123-72-8; heptylaldehyde, 111-71-7; acrolein, 107-02-8; benzaldehyde, 100-52-7; *p*-hydroxybenzaldehyde, 123-08-0; *p*-anisaldehyde, 123-11-5; *o*-nitrobenzaldehyde, 552-89-6; 5-nitrosalicylaldehyde, 97-51-8; furfural, 98-01-1; acetic acid, 64-19-7; formic acid, 64-18-6; propionic acid, 79-09-4; copper, 7440-50-8; DL-alanine, 302-72-7; DL-lysine hydrochloride, 70-53-1; DL-methionine, 59-51-8; DL-phenylalanine, 150-30-1; DL-proline, 609-36-9; DL-phenylglycine, 2835-06-5; DL-(*p*-hydroxyphenyl)glycine, 6324-01-2; DL-serine, 302-84-1; L-phenylglycine, 2935-35-5; L-(*p*-hydroxyphenyl)glycine, 32462-30-9.