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# Amino Acids and Peptides. XVI.[1] A New Synthesis of α-Phenylglycine and Its Derivatives[2]

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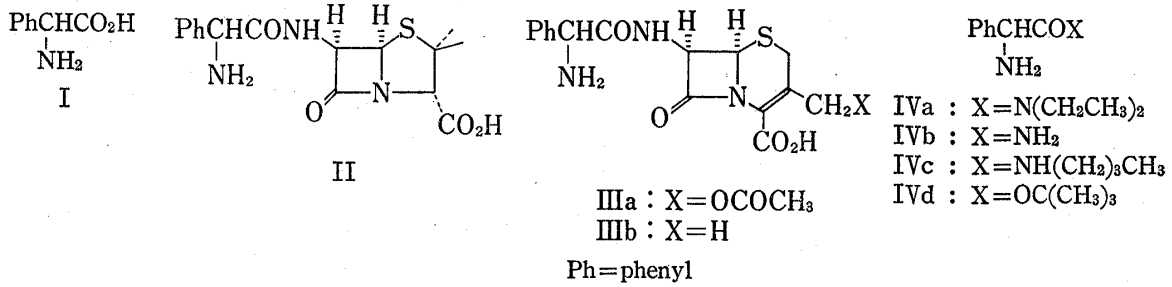
N,N-Diethyl phenylacetamide and N-*n*-butyl phenylacetamide were respectively α-lithiated, followed by amination with methoxyamine to give α-phenylglycine N,N-diethylamide (IVa) and α-phenylglycine N-*n*-butylamide (IVc). However, phenylacetamide gave phenylglyoxylamide only and *tert*-butyl phenylacetate did not undergo the above amination reaction.

Benzylisocyanide and N-(diphenylmethylene)benzylamine (VII) were respectively α-lithiated, subjected to carboxylation, followed by acid hydrolysis to give α-phenylglycine (I) in good yields.

Although α-phenylglycine (I) is neither a protein-bound amino acid nor an essential amino acid in nutrition, its importance is well known because its D-isomer constitutes a part of the widely used antibiotics with broad spectra,[4] such as ampicillin (II), cephaloglycin (IIIa) and cephalexin (IIIb), as shown in Chart 1.



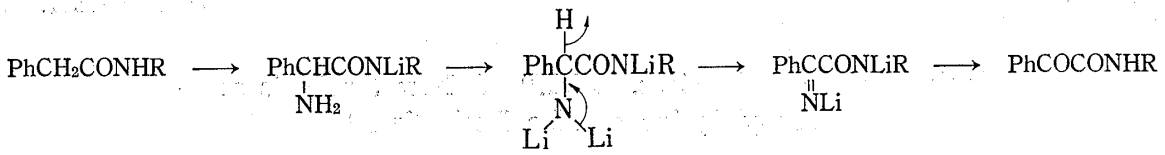

Ph=phenyl

Chart 1

We already reported[1,5] a new synthetic method for DL-α-amino acids including α-phenylglycine (I) by the amination of α-lithiated acid salts. We now report its extension to the synthesis of some derivatives (IV) of α-phenylglycine and two new methods for the synthesis of α-phenylglycine using α-carbanion derived from benzylamine.

First, N,N-diethyl phenylacetamide was α-lithiated with lithium diisopropylamide in a mixture of tetrahydrofuran and *n*-hexane as described in our previous paper,[1] and the resultant carbanion was aminated with methoxyamine which was revealed to be one of the best aminating reagent.[1,5] The aminated product (IVa) was obtained in 15% yield with 62.5% recovery of the starting amide. Phenylacetamide did not give any trace of the aminated product (IVb) under similar reaction conditions. Instead, phenylglyoxylamide was obtained though in low yield. The mechanism of its formation may be explained[1,6] as shown in Chart 2.

1) Part XV: T. Oguri, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **23**, 167 (1975).
2) Presented in part at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April, 1973, Abstracts of Papers, II 5G 9-3, p. 52.
3) Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*
4) E.H. Flynn (ed.), "Cephalosporins and Penicillins. Chemistry and Biology," Academic Press, New York and London, 1972.
5) S. Yamada, T. Oguri, and T. Shioiri, *J.C.S. Chem. Comm.*, **1972**, 623.
6) *cf.* H.G. Richey, Jr., W.F. Erickson, and A.S. Heyn, *Tetrahedron Letters*, **1971**, 2187; W.F. Erickson and H.G. Richey, Jr., *Tetrahedron Letters*, **1972**, 2811.



Ph=phenyl; R=H or *n*-Bu

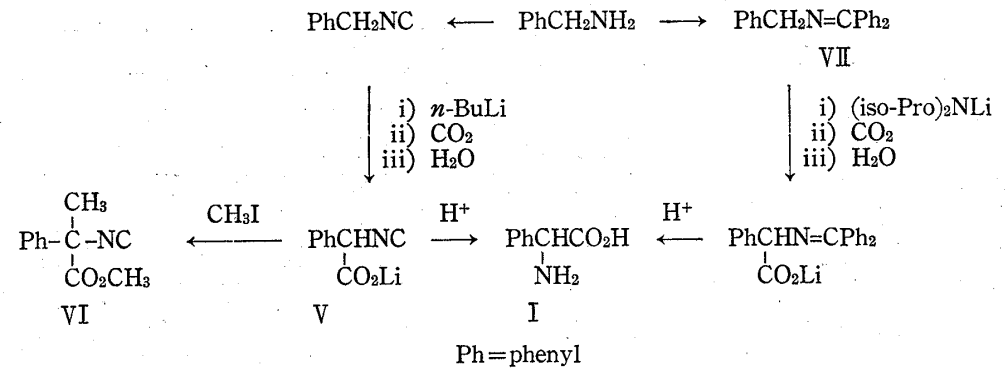
Chart 2

However, N-*n*-butyl phenylacetamide underwent the amination reaction under similar conditions (see Experimental) to give α-phenylglycine N-*n*-butylamide (IVc) in 30% yield together with N-*n*-butyl phenylglyoxylamide in 28% yield and the starting amide (26%). The formation of N-*n*-butyl phenylglyoxylamide may be analogously explained as in the case of phenylglyoxylamide. Shorter reaction time increased the yield of IVc to 49% with 37% recovery of the starting amide.

In contrast, *tert*-butyl phenylacetate was subjected to the amination reaction to give no aminated product (IVd), whereas carboxylation of the carbanion derived from *tert*-butyl phenylacetate smoothly proceeded to give *tert*-butyl hydrogen phenylmalonate in 82% yield.[7] Furthermore, similar α-carboxylation of N,N-diethyl phenylacetamide afforded 2-(N,N-diethylcarbamoyl)phenylacetic acid in good yield. This satisfactory results led us to investigate the method for the synthesis of α-phenylglycine (I) by carboxylation of α-carbanion derived from benzylamine.

Thus benzylamine was converted to benzylisocyanide,[8] which was lithiated with *n*-butyl lithium followed by bubbling of carbon dioxide gas. The product, presumably bearing the structure (V),[9,10] was hydrolyzed with aqueous acid to give α-phenylglycine (I) in 80.6% yield. After our work had been completed, a similar preparation of I by carboxylation of α-carbanion from benzylisocyanide was reported by two groups.[10] The product (V) afforded methyl 2-methyl-2-isocyanophenylacetate (VI) by treatment with methyl iodide.

On the other hand, benzylamine was converted to the Schiff base (VII) with benzophenone. Analogous treatment of VII as above afforded I in 51.6% yield as shown in Chart 3. The use of the anions of the Schiff bases derived from benzophenone in synthesis has recent precedent.[11]



Ph=phenyl

Chart 3

7) S. Reiffers, H. Wynberg, and J. Strating, *Tetrahedron Letters*, **1971**, 3001; K. Ninomiya, T. Shioiri, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **22**, 1398 (1974).
8) W.P. Weber and G.W. Gokel, *Tetrahedron Letters*, **1972**, 1637.
9) See, however, G.E. Niznik, W.H. Morrison, III, and H.M. Walborsky, *Org. Synth.*, **51**, 31 (1971).
10) W. Vaalburg, J. Strating, M.G. Woldring, and H. Wynberg, *Synth. Comm.*, **2**, 423 (1972); K. Matsumoto, M. Suzuki, and M. Miyoshi, *J. Org. Chem.*, **38**, 2094 (1973).
11) Th. Kauffmann, E. Köppelmann, and H. Berg, *Angew. Chem.*, **82**, 138 (1970); T. Cuvigny, P. Hullot, and H. Normant, *Compt. Rend.*, série C, **272**, 862 (1971); Th. Kauffmann and R. Eidenschink, *Angew. Chem. int. Ed.*, **12**, 568 (1973).

## Experimental

Melting points were measured on a hot stage apparatus and uncorrected.

Tetrahydrofuran and diisopropylamine were purified as previously described.[1] *n*-Butyl lithium was obtained from Sankyo Kasei Co. The reactions using carbanions were carried out under a nitrogen atmosphere.

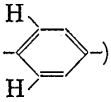
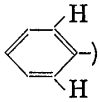
**α-Phenylglycine N,N-Diethylamide (IVa)**——To diisopropylamine (303 mg, 2.3×1.3 mmole) in tetrahydrofuran (8 ml) was added with stirring *n*-butyl lithium in *n*-hexane solution (2.5 ml of 1.2M, 2.3×1.3 mmole) below 0° (inside temperature) under nitrogen. After the mixture was stirred at −5° for 15 min, N,N-diethyl phenylacetamide[12] (440 mg, 2.3 mmole) in tetrahydrofuran (1 ml) was added at −20°, and the mixture was stirred for 30 min. After methoxyamine[1] (423 mg, 2.3×4 mmole) was added at −20°, the mixture was stirred at −20° for 2 hr and at room temperature overnight. The reaction mixture was quenched with water (a few drops), and evaporated *in vacuo* at room temperature. The residue was dissolved in benzene (50 ml), and extracted with 10% aqueous hydrochloric acid. The aqueous solution was made alkaline with potassium carbonate, and extracted with benzene. The benzene extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated *in vacuo* to give a colorless oil (76 mg). Purification by alumina (10 g) column chromatography with benzene and chloroform (1: 1) afforded IVa as a colorless oil (72 mg, 15%), IR $\nu_{max}^{CHCl_3}$ 3380, 3305, 1638 $cm^{-1}$; NMR in $CCl_4$ $\delta$ (ppm) 1.00 (6H, doublet of triplet, 2×$CH_3$), 2.38 (2H, broad singlet, $NH_2$), 3.22 (4H, multiplet, 2×$CH_2$), 4.56 (1H, multiplet, CH), 7.28 (5H, singlet, $C_6H_5$).

A mixture of the above oil (50 mg) and phenylisocyanate (30 mg) in benzene (3 ml) was stirred at room temperature for one day. Evaporation gave a white solid, which was recrystallized from ethanol to give the phenylurea derivative of IVa (34.6 mg) as colorless prisms, mp 172.5−173.5°; IR $\nu_{max}^{KBr}$ 3365, 3340, 3290 $cm^{-1}$; NMR in $CDCl_3$ $\delta$ (ppm) 1.10 (6H, triplet, $J$=6 Hz, 2×$CH_3$), 3.42 (4H, multiplet, 2×$CH_2$), 6.02 (1H, singlet, CH), 7.30 (10H, singlet, 2×$C_6H_5$ and CHN<u>H</u>), 7.94 (1H, singlet, N<u>H</u>$C_6H_5$). *Anal.* Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.10; H, 6.94; N, 12.84.

The first benzene solution was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. Drying over sodium sulfate followed by evaporation afforded the starting amide as a yellowish oil (275 mg, 62.5%).

**Amination of Phenylacetamide**——To phenylacetamide (405 mg, 3 mmole) in tetrahydrofuran (15 ml) was added with stirring *n*-butyl lithium in *n*-hexane solution (5.5 ml of 1.09M, 3×2 mmole) at −70° under a nitrogen atmosphere. After 20 min stirring, methoxyamine (424 mg, 3×3 mmole) in tetrahydrofuran (1 ml) was added at −20°. The mixture was stirred at −20——15° for 2 hr and then at room temperature overnight. Water (a few drops) was added, and the mixture was evaporated to the residue which was dissolved in benzene and ethanol (10: 1), followed by extraction with 10% aqueous hydrochloric acid. The aqueous extracts were basified with potassium carbonate, and extracted with benzene and diethyl ether. The organic layer was washed with saturated aqueous sodium chloride, and dried over sodium sulfate. Evaporation followed by washing the solid residue with benzene afforded a white solid (63 mg), identified with the starting phenylacetamide. The washings showed many spots on its thin-layer chromatogram.

The first organic layer was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride. Drying over sodium sulfate followed by evaporation afforded a mixture of oil and solid, which was washed with benzene to leave phenylacetamide (46 mg) as a white solid. Washings were concentrated and fractionated by alumina (15 g) column chromatography with chloroform. The first fraction to be eluted was phenylacetamide (15 mg). Total recovery of phenylacetamide was 124 mg (30.6%).

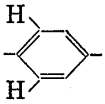
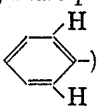
The second fraction to be eluted was phenylglyoxylamide (33 mg, 7%) as a white solid, which was recrystallized from water to give colorless crystals, mp 64—67° (lit.[13] mp 64—65°); NMR in $CDCl_3$ $\delta$ (ppm) 6.52 (2H, broad $NH_2$), 7.22—7.62 (3H, multiplet,  ), 8.18 (2H, multiplet,  ). The compound was further characterized by transformation to its 2,4-dinitrophenylhydrazone derivative, orange crystals, mp 282—283.5°, IR $\nu_{max}^{KBr}$ 3158, 1670, 1615, 1587, 1550, 1336, 864 $cm^{-1}$. *Anal.* Calcd. for $C_{14}H_{11}O_5N_5 \cdot 1/3\,H_2O$: C, 50.15; H, 3.50; N, 20.89. Found: C, 50.30; H, 3.24; N, 20.78.

**α-Phenylglycine N-*n*-Butylamide (IVc)**——(i) To lithium diisopropylamide (prepared from diisopropylamine (905 mg, 4.25×2.1 mmole) and *n*-butyl lithium in *n*-hexane solution (8.14 ml of 1.10M, 4.25×2.1 mmole)) in tetrahydrofuran (15 ml) was added N-*n*-butyl phenylacetamide[14] (812 mg, 4.25 mmole) in tetrahydrofuran (2 ml) as described in the preparation of IVa. After methoxyamine (600 mg, 4.25×3 mmole) was added, the mixture was stirred at −15——10° for 2 hr and at room temperature overnight. Water

12) R. Delaby, P. Reynaud, and F. Lilly, *Bull. Soc. Chim. France*, **1961**, 2067.
13) L. Claisen, *Ber.*, **10**, 1663 (1877).
14) O.M. Behr, G. Eglinton, I.A. Lardy, and R.A. Raphael, *J. Chem. Soc.*, **1964**, 1147.

(a few drops) was added, and the mixture was evaporated *in vacuo* at room temperature to give an oily residue which was dissolved in ethyl acetate and extracted with 10% aqueous hydrochloric acid. The aqueous layer was made alkaline with potassium carbonate, and extracted with ethyl acetate. The organic extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated *in vacuo* to furnish IVc (260 mg, 30%) as a yellow viscous oil, $bp_{0.15}$ 140°; IR $\nu_{max}^{Cap.}$ 3310, 1650, $cm^{-1}$; NMR in $CDCl_3$ $\delta$ (ppm) 0.6—1.6 (7H, multiplet, $(CH_2)_2CH_3$), 2.21 (2H, singlet, $NH_2$), 3.00 (2H, quartet, $J=7$ Hz, $NHCH_2$), 4.29 (1H, singlet, CH), 7.17 (5H, multiplet, $C_6H_5$), 7.48 (1H, triplet, $J=7$ Hz, CONH).

The product (IVc) was further characterized as follows. A mixture of IVc (100 mg, 0.485 mmole) and phenylisocyanate (57.8 mg, 0.485 mmole) in benzene (5 ml) was refluxed for 15 min. Filtration followed by evaporation afforded a colorless solid, which was recrystallized from ethanol to give the phenylurea derivative (125 mg, 79.3%) as colorless needles, mp 224—225°; IR $\nu_{max}^{KBr}$ 3345, 1730, 1630, 1550 $cm^{-1}$; NMR in $CF_3CO_2H$ $\delta$ (ppm) 0.91 (3H, triplet, $CH_3$), 1.5 (4H, multiplet, $(CH_2)_2$), 3.40 (2H, quartet, $CH_2N$), 5.62 (1H, singlet, CH), 7.3 (13H, multiplet, $3\times$NH and $2\times C_6H_5$). *Anal.* Calcd. for $C_{19}H_{23}O_2N_3$: C, 70.13; H, 7.12; N, 12.91. Found: C, 70.02; H, 7.09; N, 13.00.

The first ethyl acetate layer was washed with saturated aqueous sodium bicarbonate and saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to give a yellow viscous oil, which was subjected to a silica gel (40 g) column chromatography with benzene. The first fraction to be eluted was N-*n*-butyl phenylglyoxylamide (238 mg, 28%) as a yellow oil; IR $\nu_{max}^{Cap.}$ 3240, 1680, 1660, 1526 $cm^{-1}$; NMR in $CCl_4$ $\delta$ (ppm) 0.94 (3H, triplet, $CH_3$), 1.5 (4H, multiplet, $(CH_2)_2$), 3.30 (2H, quartet, $CH_2N$), 7.4 (4H, multiplet,  and NH), 8.3 (2H, doublet,  ). Its 2,4-dinitrophenylhydrazone derivative was prepared as usual, yellow needles, mp 206.5—207.5° (from ethanol); IR 3380, 1658, 1617, 1590, 1578, 1560, 1343, 1310, 835 $cm^{-1}$. *Anal.* Calcd. for $C_{18}H_{19}O_5N_5$: C, 56.10; H, 4.97; N, 18.17. Found: C, 55.89; H, 5.00; N, 18.53.

The second fraction to be eluted was the starting material (210 mg, 26%).

(ii) When the reaction was carried out at −15——−10° for 2.5 hr after the addition of methoxyamine and the reaction mixture was worked up as above, IVc was obtained in 47% yield with 36% recovery of the starting amide.

(iii) Shorter reaction time (−15——−10° for 15 min) gave IVc in 49% yield with 37% recovery of the starting amide.

***tert*-Butyl Hydrogen Phenylmalonate**——*tert*-Butyl phenylacetate[15] (818 mg, 4.25 mmole) was $\alpha$-lithiated with lithium diisopropylamide ($4.25\times1.5$ mmole) in tetrahydrofuran (7 ml) at −72° for 40 min. Dry carbon dioxide gas was bubbled into the lithiated solution at −23——−10° for 30 min. The reaction mixture was quenched with water (a few drops), and evaporated to the residue which was dissolved in diethyl ether. Extraction of the ethereal layer with 10% aqueous sodium hydroxide, followed by acidification of the aqueous extracts with 10% aqueous hydrochloric acid afforded white precipitates (796 mg), which were filtered, washed with cold water, and dried. The acidic aqueous layer was extracted with benzene. The benzene extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to give a colorless solid (23 mg). The total yield of *tert*-butyl hydrogen phenylmalonate was 819 mg (82%). Recrystallization from petroleum ether afforded colorless prisms, mp 104.5—105.5°; IR $\nu_{max}^{CHCl_3}$ 1732 (broad), 1146 $cm^{-1}$; NMR in $CDCl_3$ $\delta$ (ppm) 1.43 (9H, singlet, $C(CH_3)_3$), 4.50 (1H, singlet, CH), 7.30 (5H, singlet, $C_6H_5$), 9.53 (1H, singlet, $CO_2H$). *Anal.* Calcd. for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found; C, 66.19; H, 6.96.

The ethereal solution was washed with saturated aqueous sodium bicarbonate, saturated aqueous sodium chloride, and dried over sodium sulfate. Evaporation afforded a yellowish oil (103 mg, 12.6%), which was identified to be the starting material.

**N,N-Diethyl 2-Phenylmalonamic Acid**——To lithium diisopropylamide (6 mmole) in tetrahydrofuran (15 ml) was added N,N-diethyl phenylacetamide (879 mg, 6 mmole) at −20°. After stirring for 30 min, dry carbon dioxide gas was passed at −20——−10° for 30 min. The pH of the reaction mixture was adjusted to 7 with 10% aqueous hydrochloric acid. The evaporated residue was treated with diethyl ether and 10% aqueous sodium hydroxide. The aqueous layer was made acidic with 10% aqueous hydrochloric acid to give white precipitates, which were filtered, washed with cold water, and dried. N,N-Diethyl 2-phenylmalonamic acid weighed 1.003 g (71%), mp 91.5—92.5° (lit.[16] 91—92°); IR $\nu_{max}^{Nujol}$ 1760, 1603 $cm^{-1}$; NMR in $CDCl_3$ $\delta$ (ppm) 1.05 (6H, quintet, $2\times CH_3$), 2.9—3.8 (4H, multiplet, $2\times CH_2$), 4.58 (1H, singlet, CH), 7.32 (5H, singlet, $C_6H_5$), 11.97 (1H, broad singlet, $CO_2H$).

**$\alpha$-Phenylglycine (I)**——(i) From Benzylisocyanide: To benzylisocyanide[8] (527 mg, 4.5 mmole) in tetrahydrofuran (15 ml) was added *n*-butyl lithium in *n*-hexane solution (8.3 ml of 1.09M, $4.5\times2$ mmole) at −70°, and the mixture was stirred for 15 min. Dry carbon dioxide gas was bubbled for 30 min. Quen-

15) D.L. Yabroff and C.W. Porter, *J. Am. Chem. Soc.*, **54**, 2453 (1932).
16) F.F. Blicke and H. Zinnes, *J. Am. Chem. Soc.*, **77**, 4849 (1955).

ching with water (a few drops) and evaporation *in vacuo* at room temperature gave V as a yellow-green solid (1.482 g).

A mixture of the crude V (1.155 g) and 10% aqueous hydrochloric acid (8 ml) was refluxed for 1.5 hr, washed with benzene, and concentrated to 5 ml *in vacuo*. The aqueous solution was adjusted to pH 6 with 10% aqueous sodium hydroxide. The white precipitates of α-phenylglycine (I) were filtered, washed with cold water and ethanol, and dried. It weighed 475 mg, the purity of which was shown to be 90% by an amino acid analyzer[1,5] (80.6% yield).

(ii) From N-(Diphenylmethylene)benzylamine (VII): To lithium diisopropylamide ($2 \times 1.1$ mmole) in tetrahydrofuran (10 ml) was added N-(diphenylmethylene)benzylamine[17] (VII) (542 mg, 2 mmole) in tetrahydrofuran (2 ml) at −70——50°. After stirring for 15 min, dry carbon dioxide gas was bubbled at −70——50° for 20 min. The mixture was quenched with water (a few drops), and evaporated *in vacuo* to give a slightly yellow solid (715 mg). A part of this solid (465 mg) was refluxed with 10% aqueous hydrochloric acid (4 ml) for 30 min. The reaction mixture was diluted with water (20 ml) and extracted with benzene. The benzene extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated *in vacuo* to give benzophenone (204 mg, 86.5%) as colorless needles, identified by spectral and thin-layer chromatographic comparisons.

The aqueous layer was concentrated *in vacuo* to 3 ml, and adjusted to pH 6 with 10% aqueous sodium hydroxide. The white precipitates were filtered, washed with cold water and ethanol, and dried. α-Phenylglycine (I) thus obtained weighed 127 mg, whose purity was proved to be 79.5% by an amino acid analyzer (51.6% yield).

**Methyl 2-Methyl-2-isocyanophenylacetate (VI)**——A mixture of the crude V (200 mg) obtained as above and methyl iodide (0.6 ml) in dimethylacetamide (2 ml) was stirred at room temperature for 2 days. The mixture was diluted with benzene, washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to give a brown oil (120 mg). Purification by a silica gel preparative layer chromatography with benzene afforded VI (53 mg) as a colorless oil, $bp_7$ 117°; IR $\nu_{max}^{Cap.}$ 2120, 1748 $cm^{-1}$; NMR in $CCl_4$ $\delta$ (ppm) 1.98 (3H, singlet, C–$CH_3$), 3.72 (3H, singlet, $CO_2CH_3$), 7.4 (5H, multiplet, $C_6H_5$). *Anal.* Calcd. for $C_{11}H_{11}O_2N$: C, 69.82; H, 5.86; N, 7.40. Found: C, 69.86; H, 5.79; N, 7.58.

**Acknowledgement** We wish to thank Prof. Y. Ogihara of our Faculty for amino acid analysis.

17) G. Reddelien, *Ber.*, **53**, 334 (1920).