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Amino Acids and Peptides. XV.[1] A New Synthesis of α-Amino Acids by Amination of α-Metalated Carboxylic Acids[2]

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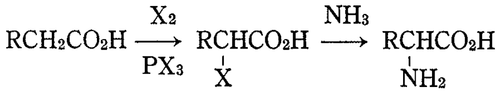
Amination of α-lithiated carboxylic acid salts was investigated using isovaleric acid mainly. Methoxyamine bearing a proper electronic character was the best aminating reagent, as shown in Table I. Several α-amino acids, *e.g.*, valine, leucine, methionine, phenylalanine, and α-phenylglycine, were prepared by this new method, summarized in Table II. The synthesis of two new aminating reagents, 3,5-dinitromesitoxyamine and 2-tetrahydropyranyloxyamine were described.

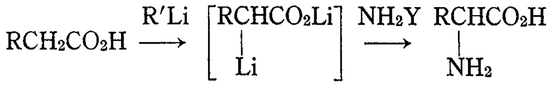
One of the general methods for the synthesis of racemic α-amino acids is α-halogenation of the carboxylic acids containing their full carbon skeleton, followed by reaction with ammonia:



$$\mathrm{RCH_2CO_2H} \xrightarrow[\mathrm{PX_3}]{\mathrm{X_2}} \underset{\mathrm{X}}{\mathrm{RCHCO_2H}} \xrightarrow{\mathrm{NH_3}} \underset{\mathrm{NH_2}}{\mathrm{RCHCO_2H}}$$

X: halogen

This method involves two-step process in acidic and alkaline mediums. Recent developments of synthetic use of metalated carboxylic acids[4] prompted us to attempt the direct introduction of an amino group into the α-position of carboxylic acids, which would be expected to be a better substitute for the above classical method.[5] The general scheme is depicted as follows:



$$\mathrm{RCH_2CO_2H} \xrightarrow{\mathrm{R'Li}} \left[\underset{\mathrm{Li}}{\mathrm{RCHCO_2Li}}\right] \xrightarrow{\mathrm{NH_2Y}} \underset{\mathrm{NH_2}}{\mathrm{RCHCO_2H}}$$

Y: leaving group

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[1] Part XIV: N. Takamura, T. Mizoguchi, K. Koga, and S. Yamada, *Tetrahedron*, "in press."

[2] Preliminary communication: S. Yamada, T. Oguri, and T. Shioiri, *J. Chem. Soc. Chem. Comm.*, **1972**, 623. Presented in part at the 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April, 1972.

[3] Location: *7-3-1, Hongo, Bunkyo-ku, Tokyo, 113, Japan.*

[4] *a*) P.L. Creger, *J. Am. Chem. Soc.*, **89**, 2500 (1967); *idem*, *Org. Synth.*, **50**, 58 (1970); *b*) P.L. Creger, *J. Am. Chem. Soc.*, **92**, 1396, 1397, (1970); *c*) P.L. Creger, *Tetrahedron Letters*, **1972**, 79; *d*) P.L. Creger, *J. Org. Chem.*, **37**, 1907 (1972); *e*) P.E. Pfeffer and L.S. Silbert, *J. Org. Chem.*, **35**, 262 (1970); *f*) P.E. Pfeffer and L.S. Silbert, *Tetrahedron Letters*, **1970**, 699; *g*) P.E. Pfeffer and L.S. Silbert, *J. Org. Chem.*, **36**, 3290 (1971); *h*) P.E. Pfeffer, L.S. Silbert, and J.M. Chirinko, Jr., *J. Org. Chem.*, **37**, 451 (1972); *i*) P.E. Pfeffer, E. Kinsel, and L.S. Silbert, *J. Org. Chem.*, **37**, 1256 (1972); *j*) P.E. Pfeffer, L.S. Silbert, and E. Kinsel, *Tetrahedron Letters*, **1973**, 1163; *k*) G.W. Moersch and A.R. Burkett, *J. Org. Chem.*, **36**, 1149 (1971); *l*) G.W. Moersch and M.L. Zwiesler, *Synthesis*, **1971**, 647; *m*) Y.N. Kuo, J.A. Yahner, and C. Ainsworth, *J. Am. Chem. Soc.*, **93**, 6321 (1971); *n*) S. Watanabe, K. Suga, T. Fujita, and K. Fujiyoshi, *Chem. and Ind.*, **1972**, 80; *o*) G. Cainelli, G. Cardillo, and A. U. Ronchi, *J. Chem. Soc. Chem. Comm.*, **1973**, 94; *p*) G.K. Koch and J.M.M. Kop, *Tetrahedron Letters*, **1974**, 603.

[5] Amination of α-carbanions derived from some carboxylic acid esters has been reported; *a*) M. Horiike, J. Oda, Y. Inouye, and M. Ohno, *Agr. Biol. Chem.*, **33**, 292 (1969); *b*) T. Sheradsky, G. Salemnick, and Z. Nir, *Tetrahedron*, **28**, 3833 (1972); *c*) Y. Tamura, S. Kato, and M. Ikeda, *Chem. & Ind.*, **1971**, 767.

First, α-lithiation of isovaleric acid was carried out with lithium diisopropylamide in a mixture of tetrahydrofuran and *n*-hexane using hexamethylphosphortriamide as a cosolvent,[4i] and several aminating reagents (NH_2Y)[6] were investigated to prepare valine from isovaleric acid, as shown in Table I.

Although 2,4-dinitrophenoxyamine has been reported[5b] as a reagent for aminating a few carbanions, it was immediately decomposed at −15° under the reaction conditions shown in Experimental. Reaction at −70° also did not give any appreciable amount of valine. Thus 3,5-dinitromesitoxyamine was chosen as an aminating reagent, having a better leaving group and being possibly more stable to the reaction conditions. Preparation of 3,5-dinitromesitoxyamine was carried out from mesitoic acid by successive treatment with fuming nitric acid, thionyl chloride, *tert*-butyl N-hydroxycarbamate, and hydrogen chloride, as shown in Chart 1.

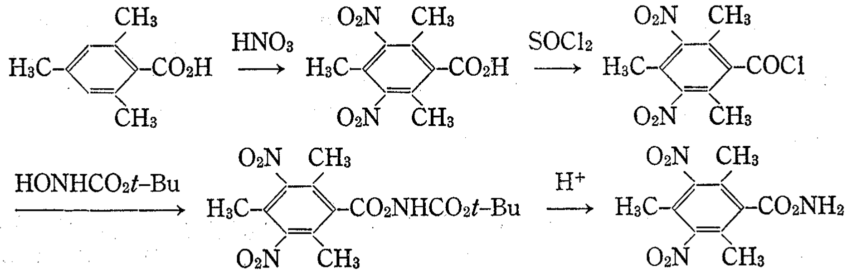
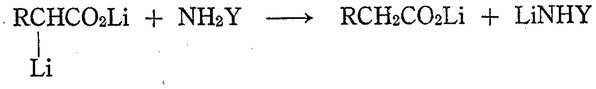


Chart 1

The amination of α-lithiated isovaleric acid with 3,5-dinitromesitoxyamine, however, afforded valine in only 5.3% yield. The reason for this discouraging result may be that the exchange reaction between lithium ion and proton at the amino group will be apt to occur competitively owing to the increase of the acidity of the amino group, while the nucleophilic attack of the carbanion to the amino group will be facilitated by the introduction of a better leaving group to the amino function.



$$\underset{\substack{|\\ \text{Li}}}{\text{RCH}}\text{CO}_2\text{Li} + \text{NH}_2\text{Y} \longrightarrow \text{RCH}_2\text{CO}_2\text{Li} + \text{LiNHY}$$

Accordingly, the leaving group was replaced by much weaker ones, such as methyl, ethyl, isopropyl, and *tert*-butyl groups. The yields of amination, however, diminished with increasing the electron-donating character because of the lower electrophilicity of the nitrogen atom. Methoxyamine bearing a proper electronic character was the best aminating reagent to afford valine in 33.9% yield using lithium diisopropylamide, which was found to be superior to lithium N-isopropylcyclohexylamide recently recommended by Rathke and Lindert[7] for the formation of lithium ester enolates and to a combination of N,N,N′,N′-tetramethylethylenediamine and *n*-butyl lithium.[8] Benzyloxyamine, hydroxylamine-*O*-sulfonic acid, monochloramine, and mesitoxyamine were also less efficient aminating reagents than methoxyamine.

The new amination method using methoxyamine was applied to the synthesis of a few α-amino acids. Leucine, methionine, and phenylalanine were obtained in about 10% yield by the amination of isocaproic acid, 4-methylthiobutyric acid, and 3-phenylpropionic acid,[9] respectively, assembled in Table II.

Next, our attention was directed to the amination of phenylacetic acid, which will furnish α-phenylglycine, a constituent of important antibiotics, ampicillin and cephalexin.[10] The

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6) See a review, Y. Tamura and M. Ikeda, *Yuki Gosei Kagaku Kyokai Shi*, **32**, 136 (1974).

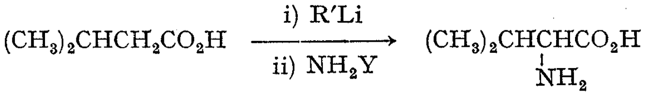
7) M.W. Rathke and A. Lindert, *J. Am. Chem. Soc.*, **93**, 2318 (1971).

8) C. Agami, *Bull. Soc. Chim. France*, **1970**, 1619.

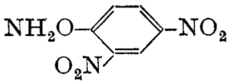
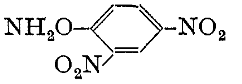
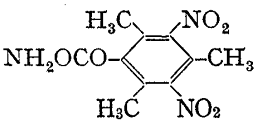
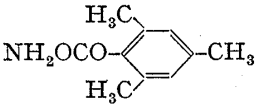
9) Although the yield of amination was somewhat lower, 3-phenylpropionic acid was alkylated at the α-position with *n*-butyl bromide in 76% yield.

10) E.H. Flynn (ed.), "Cephalosporins and Penicillins. Chemistry and Biology," Academic Press, New York and London, 1972.

Table I. α-Amination of Isovaleric Acid



$$(CH_3)_2CHCH_2CO_2H \xrightarrow[\text{ii) } NH_2Y]{\text{i) } R'Li} (CH_3)_2CH\underset{NH_2}{\underset{|}{C}}HCO_2H$$

Metalating reagent	Aminating reagent	Reaction temp. (°C)	Reaction time (hr)	Yield[a] (%)
(iso-Pro)$_2$NLi		−15—−10 room temp.	2 overnight	—
(iso-Pro)$_2$NLi		−74—−60 room temp.	2 overnight	0
(iso-Pro)$_2$NLi		−15—−10 room temp.	2 overnight	5.3
(iso-Pro)$_2$NLi	NH_2OCH_3	−15—−10 room temp.	2 overnight	33.9 (27.5)[b]
(iso-Pro)$_2$NLi	NH_2OCH_3	room temp.	overnight	24.7
(iso-Pro)\\ NLi Cyclohexyl/	NH_2OCH_3	−15—−10 room temp.	2 overnight	32.0
CH_2NMe_2 $\vert$ CH_2NMe_2 -n-BuLi	NH_2OCH_3	−15—−10 room temp.	2 overnight	trace
(iso-Pro)$_2$NLi	$NH_2OCH_2CH_3$	−15—−10 room temp.	2 overnight	22.4
(iso-Pro)$_2$NLi	$NH_2OCH(CH_3)_2$	−15—−10 room temp.	2 overnight	25.4
(iso-Pro)$_2$NLi	$NH_2OC(CH_3)_3$	−15—−10 room temp.	2 overnight	18.3
(iso-Pro)$_2$NLi	NH_2OCH_2Ph	−74—−60 room temp.	2 overnight	trace
(iso-Pro)$_2$NLi	NH_2OSO_3H	−74—−60 room temp.	2 overnight	trace
(iso-Pro)$_2$NLi	NH_2Cl	−74—−60 room temp.	2 overnight	7.7
(iso-Pro)$_2$NLi		−74—−60 room temp.	2 overnight	4.3

a) Yields were determined by an amino acid analyzer, unless otherwise stated.
b) isolated yield
Ph=phenyl

analogous procedure using lithium diisopropylamide and methoxyamine afforded α-phenylglycine in 23.5% yield, accompanied by benzoic acid in 29% yield. The formation of the latter may be explained as follows; (i) the amino group of α-phenylglycine once formed is lithiated, (ii) lithium hydride is eliminated from the lithiated α-phenylglycine, (iii) the resultant α-imino acid is subjected to hydrolysis to give phenylglyoxylic acid during work-up, followed by (iv) decarbonylation from phenylglyoxylic acid, as shown below:

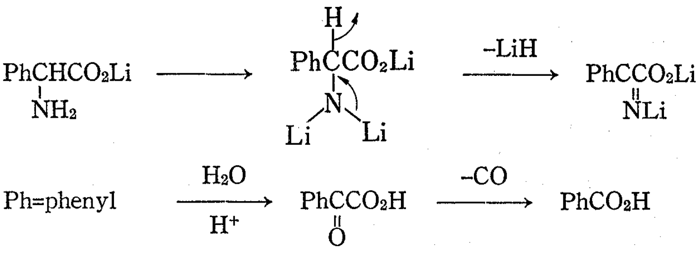
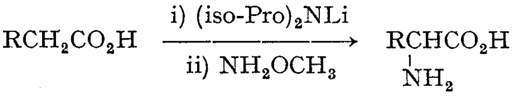
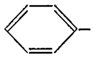
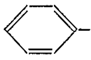
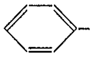
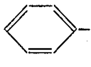


TABLE II. α-Amination of Carboxylic Acids



$$RCH_2CO_2H \xrightarrow[\text{ii) } NH_2OCH_3]{\text{i) (iso-Pro)}_2NLi} \underset{NH_2}{\underset{|}{RCHCO_2H}}$$

Carboxylic acid	Reaction temp. (°C)	Reaction time (hr)	α-Amino acid	Yield[a] (%)
$(CH_3)_2CH(CH_2)_2CO_2H$	−15—−10 room temp.	2 overnight	leucine	10.8
$CH_3S(CH_2)_3CO_2H$	−15—−10 room temp.	2 overnight	methionine	8.6
 $-(CH_2)_2CO_2H$	−15—−10 room temp.	2 overnight	phenylalanine	6.9
 $-CH_2CO_2H$	−15—−10 room temp.	2 overnight	α-phenylglycine	(23.5)[b,c]
 $-CH_2CO_2H$	−15—−10	2	α-phenylglycine	(55.5)[b,d]
 $-CH_2CO_2H$	−15—−10	2	α-phenylglycine	(46.2)[b,e]

a) Yields were determined by an amino acid analyzer, unless otherwise stated.
b) isolated yield
c) benzoic acid (29%) and recovery of the starting acid (20.7%)
d) recovery of the starting acid (32.8%)
e) 2-Tetrahydropyranyloxyamine was used instead of methoxyamine.

In fact, α-phenylglycine afforded both phenylglyoxylic acid and benzoic acid under the reaction conditions similar to the α-amination reaction.[11] However, the shorter reaction time yielded α-phenylglycine in 55.5% yield, accompanied by the recovery of the starting acid in 32.8% yield.

In this case, we tried another new aminating reagent, 2-tetrahydropyranyloxyamine, giving α-phenylglycine from phenylacetic acid in 46.2% yield. 2-Tetrahydropyranyloxyamine was prepared by the addition of N-hydroxysuccinimide to 2,3-dihydro-4H-pyran, followed by hydrazinolysis,[12] as shown in Chart 2.

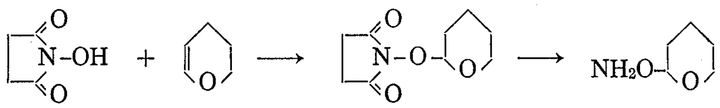


Chart 2

Experimental

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

Materials

Tetrahydrofuran was distilled from lithium aluminum hydride under nitrogen prior to use. Diisopropylamine was distilled from calcium hydride. Hexamethylphosphortriamide was distilled from sodium hydride under reduced pressure. *n*-Butyl lithium (1.1—1.9M in *n*-hexane solution) was obtained from Sankyo Kasei Co.

Aminating Reagents

2,4-Dinitrophenoxyamine,[5b,13] methoxyamine,[14,15] ethoxyamine,[14] isopropoxyamine,[14] *tert*-butoxy-

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[11] *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.

[12] *cf.* R.N. Warrener and E.N. Cain, *Angew. Chem.*, **78**, 491 (1966).

[13] T. Sheradsky, *J. Heterocyclic Chem.*, **4**, 413 (1967).

[14] W. Theilacker and K. Ebke, *Angew. Chem.*, **68**, 303 (1956); W. Theilacker and E. Wegner, "Newer Methods of Preparative Organic Chemistry," Vol. III, ed. by W. Foerst, Academic Press, New York and London, 1964, p. 303.

[15] H. Hjeds, *Acta. Chem. Scand.*, **19**, 1764 (1965).

amine,14) benzyloxyamine,14) hydroxylamine-*O*-sulfonic acid,16) monochloramine,17) and mesitoxyamine18) were prepared according to the literatures.

3,5-Dinitromesitoxyamine——(i) To fuming nitric acid (70 ml) was added mesitoic acid19) (7 g, 0.043 mole) at 0—5°. The mixture was stirred at room temperature overnight, and poured into ice-water (250 ml). The resultant white precipitates were filtered, dried, and recrystallized from benzene to give 3,5-dinitromesitoic acid (8.25 g), mp 180—235°, which were contaminated with a little amount of mononitro derivative.

(ii) A mixture of the crude nitrated mesitoic acid (40 g) and thionyl chloride (56.5 g) in benzene (320 ml) was refluxed for 3 hr. Evaporation followed by recrystallization from benzene afforded 3,5-dinitromesitoyl chloride (34.6 g, 80%) as colorless needles, mp 154—158° (lit.20) 154—155°), IR $\nu_{\text{max}}^{\text{Nujol}}$ 1800, 1530, 1365 cm^{-1}.

(iii) *tert*-Butyl N-hydroxycarbamate21) (2.72 g, 0.01 mole) in methylene chloride (5 ml) was added to an ice-cooled mixture of the above chloride (1.33 g, 0.01 mole) and triethylamine (1.21 g, 0.012 mole) in methylene chloride (7 ml) during 1.5 hr. The mixture was stirred with ice-cooling for 4 hr, and then at room temperature overnight. Washing the mixture with water (2 × 5 ml), drying over sodium sulfate followed by evaporation afforded a colorless solid (3.45 g), which was recrystallized from ligroin to give *tert*-butyl N-(3,5-dinitromesitoyl)oxycarbamate (1.35 g, 36.7%) as colorless prisms, mp 152—154°; IR $\nu_{\text{max}}^{\text{CHCl}_3}$ 3342, 1782, 1758, 1539, 1360, 874 cm^{-1}; NMR in $CDCl_3$ δ (ppm) 1.52 (9H, singlet, *tert*-butyl), 2.22 (3H, singlet, 4-CH_3), 2.34 (6H, singlet, 2- and 6-CH_3), 8.14 (1H, singlet, NH). *Anal.* Calcd. for $C_{15}H_{19}O_8N_3$: C, 48.78; H, 5.19; N, 11.38. Found: C, 48.77; H, 5.24; N, 11.25.

(iv) To the above oxycarbamate (10.74 g, 0.029 mole) in nitromethane (120 ml) was bubbled dry hydrogen chloride gas for 7 min. The mixture was stirred for 15 min to give colorless precipitates, which were filtered and dried. The dried material (8.45 g) was suspended in water (60 ml). After addition of diethyl ether, the mixture was made alkaline with saturated aqueous sodium bicarbonate to precipitate a white solid (5.45 g). The ethereal layer was washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated to leave a white solid (1.47 g). The combined solid was chromatographed over alumina (200 g) with a mixture of chloroform and *n*-hexane (1: 1) to give 3,5-dinitromesitoxyamine as a colorless solid (3.97 g, 50.7%). Recrystallization from ethanol gave colorless needles, mp 150—153° (decomp.); IR $\nu_{\text{max}}^{\text{KBr}}$ 3291, 3200, 1745, 1524, 1360, 874 cm^{-1}; NMR in $CDCl_3$ δ (ppm) 2.22 (3H, singlet, 4-CH_3), 2.26 (6H, singlet, 2- and 6-CH_3), 5.70 (2H, broad singlet, NH). *Anal.* Calcd. for $C_{10}H_{11}O_2N$: C, 44.61; H, 4.12; N, 15.61. Found: C, 44.66; H, 4.08; N, 15.46.

2-Tetrahydropyranyloxyamine——(i) A mixture of N-hydroxysuccinimide (5.75 g, 0.05 mole), 2,3-dihydro-4H-pyran (6.30 g, 0.075 mole), and phosphorus oxychloride (5 drops) in tetrahydrofuran (50 ml) was stirred at room temperature overnight. Evaporation followed by recrystallization from tetrahydrofuran afforded N-(2-tetrahydropyranyloxy)succinimide (5.79 g, 58.1%) as colorless needles, mp 125.5—126.5°; IR $\nu_{\text{max}}^{\text{KBr}}$ 1778, 1722 cm^{-1}; NMR in $CDCl_3$ δ (ppm) 1.7 (6H, multiplet, 3,4,5-CH_2 protons of pyran), 2.7 (4H, singlet, CH_2 protons of succinimide), 3.5, 4.4 (2H, pair of multiplet, 6-CH_2 protons of pyran), 5.3 (1H, multiplet, 2-CH proton of pyran). *Anal.* Calcd. for $C_9H_{13}O_4N$: C, 54.26; H, 6.58; N, 7.03. Found: C, 54.24; H, 6.59; N, 7.11.

(ii) A mixture of N-(2-tetrahydropyranyloxy)succinimide (4.35 g, 0.022 mole) and 90% aqueous hydrazine hydrate (1.21 g, 0.022 mole) in benzene (5 ml) was refluxed overnight, giving white precipitates. The filtrate was evaporated to the residue, which was distilled at 86—87° (23 mmHg) (lit.12) bp_{23}83°) to furnish 2-tetrahydropyranyloxyamine (1.97 g, 76.7%) as a colorless oil. The oil was crystallized by allowing to stand in a freezer, mp 34—35.5°; IR $\nu_{\text{max}}^{\text{KBr}}$ 3320, 3240 cm^{-1}; NMR in $CDCl_3$ δ (ppm) 1.6 (6H, multiplet, 3,4,5-CH_2 protons of pyran), 3.70 (2H, multiplet, 6-CH_2 protons of pyran), 4.68 (1H, multiplet, CH), 5.27 (2H, singlet, NH_2).

α-Anion Preparation

The following procedure is typical of the general method.

To diisopropylamine (1.03 g, 4.25 × 2.4 mmole) in tetrahydrofuran (7.3 ml) was added with stirring *n*-butyl lithium in *n*-hexane solution (7.1 ml. of 1.44M, 4.25 × 2.4 mmole) below 0° (inside temperature) under a nitrogen atmosphere. After the mixture was stirred at −5° for 15 min, a carboxylic acid (4.25 mmole) in tetrahydrofuran (1 ml) was added at −15—−10°, and the white suspension was stirred for 15 min. Hexamethylphosphortriamide (1.8 ml, 10 mmole) was added, and the mixture was stirred at 5° for 15 min, giving a yellow homogeneous solution.

Preparation of *α*-Amino Acids from Carboxylic Acids

To the dianion solution of a carboxylic acid prepared as above was added an aminating reagent (4.25 × 3 mmole) at either −15—−10° or −74—−60°, and the mixture was stirred at either −15—−10° or −74—−60°

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16) H.J. Matsuguma and L.F. Audrieth, *Inorg. Synth.*, **5**, 122 (1957).

17) G.A. Jaffari and A.J. Nunn, *J. Chem. Soc.* (C), **1971**, 823.

18) L.A. Carpino, *J. Am. Chem. Soc.*, **82**, 3133 (1960); L.A. Carpino, *J. Org. Chem.*, **29**, 2820 (1964).

19) D.M. Bowen, "Organic Syntheses.," Coll. Vol. 3, ed. by E.C. Horning, John Wiley and Sons, Inc. New York, 1955, p. 553.

20) F. Kunckell and A. Hildebrandt, *Ber.*, **34**, 1826 (1901).

21) L.A. Carpino, C.A. Giza, and B.A. Carpino, *J. Am. Chem. Soc.*, **81**, 955 (1959).

for 2 hr, and then at room temperature overnight. Reaction conditions of each case were shown in Tables I and II.

The reaction mixture was quenched with several drops of water, and evaporated *in vacuo* at room temperature. The residue was dissolved in water (80 ml), and the solution was washed with chloroform (5×20 ml). The aqueous layer was diluted to 100 ml accurately, and 1 ml of them was again diluted to 50 ml, which was subjected to an amino acid analysis.

Valine——The above aqueous layer diluted to 100 ml was concentrated, and passed the ion exchange resin (Amberlite IR-120, 52 ml) with 5% aqueous ammonia eluant. Evaporation afforded a brownish white powder of valine, identified by an amino acid analyzer.

α-Phenylglycine——After washing the aqueous solution with chloroform as above, the solution was concentrated to 5 ml, and was adjusted to pH 6 with 10% aqueous hydrochloric acid. The white precipitates of α-phenylglycine was filtered, washed with water, and dried. The purity was checked with an amino acid analyzer. The crude α-phenylglycine was further confirmed by its conversion to the phenylurea derivative as follows.

To a mixture of the crude α-phenylglycine (0.151 g, 1 mmole) and sodium hydroxide (85% pure, 0.047 g, 1 mmole) in water (2 ml) was added phenyl isocyanate (0.119 g, 1 mmole) with stirring. After stirring at room temperature for 3 hr, phenyl isocyanate (0.08 g, 0.7 mmole) was added, and the mixture was stirred for 1 hr. Filtration followed by being adjusted to pH 1—2 with 10% hydrochloric acid afforded white precipitates, which were filtered, washed with water, and dried. Recrystallization from aqueous ethanol afforded N-(N-phenylcarbamoyl)-α-phenylglycine (0.20 g, 74%) as colorless needles, mp 171—172.5°; IR $\nu_{\max}^{\text{KBr}}$ 3345, 1730, 1630, 1550 cm^{-1}; NMR in CF_3CO_2H δ (ppm) 5.48 (1H, doublet, $J=12$ Hz, CH), 7.1—7.7 (13H, multiplet, $2\times C_6H_5$, $2\times$NH, CO_2H). *Anal.* Calcd. for $C_{15}H_{14}O_3N_2\cdot 1/2\ H_2O$: C, 64.50; H, 5.41; N, 10.03. Found: C, 64.23; H, 5.45; N, 9.85.

α-Phenylglycine and Benzoic Acid——The dianion of phenylacetic acid (4.25 mmole) was prepared with lithium diisopropylamide, and aminated with methoxyamine at −15——10° for 2 hr, and then at room temperature overnight. After work-up as above, α-phenylglycine was obtained in 23.5% yield (0.163 g, 92.5% pure) from the aqueous layer by the precipitation at the isoelectric point. The mother liquor was acidified with 10% aqueous hydrochloric acid to pH 1—2, and extracted with diethyl ether. The ethereal extracts were washed with saturated aqueous sodium chloride, dried, and evaporated to leave a brown foam (0.30 g), which was fractionated by a silica gel (Wakogel C-200, 30 g) column chromatography with benzene. The first fraction to be eluted was benzoic acid (0.15 g, 29%) as colorless leaflets (recrystallized from a mixture of benzene and *n*-hexane), mp 122—123°, identified with the authentic specimen of commercial origin. The second fraction to be eluted was phenylacetic acid (0.12 g, 20.7%).

Benzoic Acid and Phenylglyoxylic Acid from α-Phenylglycine——To lithium diisopropylamide (8.5×2.4 mmole) in tetrahydrofuran (14.6 ml) was added α-phenylglycine (1.29 g, 8.5 mmole) suspended in a mixture of hexamethylphosphortriamide (3.6 ml) and tetrahydrofuran (6 ml) under a nitrogen atmosphere. The mixture was stirred at −15——10° for 2 hr, and then at room temperature overnight. After work-up as above, the carboxylic acid fraction (0.21 g) was obtained from the ethereal extracts, and fractionated by a silica gel (Wakogel C-200, 10 g) column chromatography with benzene. The first fraction to be eluted was benzoic acid (0.04 g). The second fraction to be eluted was α-phenylglyoxylic acid (0.10 g), which was identified as the 2,4-dinitrophenylhydrazone derivative, orange prisms (recrystallized from ethanol), mp 195—196° (decomp.) (lit.[22]) 197—199°). *Anal.* Calcd. for $C_{14}H_{10}O_6N_4$: C, 50.91; H, 3.05; N, 16.97. Found; C, 50.63; H, 3.23; N, 16.90.

Alkylation of 3-Phenylpropionic Acid; 2-Benzylhexanoic Acid——To the dianion prepared from lithium diisopropylamide (6×2.2 mmole) and 3-phenylpropionic acid (0.90 g, 6 mmole) in tetrahydrofuran (6.2 ml) according to the general procedure was added *n*-butyl bromide (2.47 g, 6×3 mmole) at −10°. The mixture was stirred at −10° for 2 hr, and at room temperature overnight. After being quenched with water (1 ml), the mixture was concentrated, poured into ice-water, acidified with 10% aqueous hydrochloric acid to pH 1—2, and extracted with diethyl ether. The ethereal extracts were washed with saturated aqueous sodium chloride, dried over sodium sulfate, and evaporated. Distillation of the residue at 158—162° (2 mmHg) afforded an oil, which was further purified by a silica gel (Wakogel C-200, 80 g) column chromatography with diethyl ether and *n*-hexane (1: 3) to give 2-benzylhexanoic acid (0.92 g, 75.5%) as a yellowish oil (lit.[23]) $bp_{0.3}$ 127—130°); IR $\nu_{\max}^{\text{cap.}}$ 1709 cm^{-1}; NMR in $CDCl_3$ δ (ppm) 0.6—1.9 (9H, pair of multiplet, C_4H_9), 2.63 (1H, multiplet, CH), 2.81 (2H, doublet, $J=5$ Hz, $\underline{CH_2}C_6H_5$), 7.17 (5H, singlet, C_6H_5), 10.92 (1H, broad singlet, CO_2H, disappeared by D_2O exchange).

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