ml of pyridine which was cooled to −10° was added 8.43 g (0.00465 mol) of *p*-toluenesulfonyl chloride.[10] After the addition was complete, 15 g (0.00353 mol) of **2a** was added in five portions over a 15-min period. After stirring at −10° for 1 hr, the solution was left at 5° overnight and then poured into 2 l. of water with stirring, and the solid which separated was collected, washed with water, and dried, giving 18.6 g (71.5%) of **2f**: mp 80–83°; $[\alpha]^{25}D$ +22.4° (*c* 1, DMF).

Anal. Calcd for $C_{25}H_{31}NO_{10}S$: C, 55.85; H, 5.81; S, 5.97. Found: C, 55.89; H, 5.76; S, 5.82.

Methyl 2-Benzamido-2-6-dideoxy-6-fluoro-3-*O*-[D-1-(methoxycarbonyl)ethyl]-β-D-glucopyranoside (3b).—A solution of 2.5 g (4.65 mmol) of **2f** and 1.46 g (5.6 mmol) of tetrabutylammonium fluoride in 100 ml of dry methyl ethyl ketone was refluxed overnight. The solvent was removed and the residue was triturated with water. A gum formed (**3b**), which was collected and dried and recrystallized from isopropyl alcohol: yield 1.074 g (60%); mp 184–186°; $[\alpha]^{25}D$ +46.1° (*c* 1, DMF); nmr (DMSO) δ 1.25–1.38 (d, 3, CH_3–), 2.40 (s, 3, CH_3OC–), 3.30 (s, 3, CH_3OC–), and 3.38 (s, 2, CH_2F).

Anal. Calcd for $C_{18}H_{24}FNO_7$: N, 3.64; F, 4.94. Found: N, 3.55; F, 5.04.

2-Amino-2,6-dideoxy-6-fluoro-3-*O*-(D-1-carboxyethyl)-D-glucopyranose Hydrochloride (4).—A mixture of 2.2 g (5.72 mmol) of **3b** and 5 ml of 3 *N* HCl was heated on a steam bath with stirring for 4 hr.[8] The brown solution was cooled in an ice bath for 30 min and the benzoic acid was separated by filtration. The filtrate was decolorized with charcoal, the solution obtained by filtration was concentrated to dryness, and the residue was heated with 50 ml of acetone. The undissolved solid was removed by filtration, the gummy material obtained by removal of the solvent was triturated with ether, and the resulting solid was collected and dried. A 1.2-g yield (85.7%) of material was obtained which could not be recrystallized and was hygroscopic, $[\alpha]^{25}D$ +64.1° (*c* 1, DMF).

Anal. Calcd for $C_9H_{16}FNO_6 \cdot HCl$: N, 4.83; Cl, 12.25. Found: N, 3.47; Cl, 11.65.

Methyl 2-Benzamido-2,6-dideoxy-6-iodo-3-*O*-(D-1-carboxyethyl)-D-glucopyranoside 4-Lactone (5a).—A solution of 2.5 g (4.34 mmol) of **2f** and 5 g (33.0 mmol) of sodium iodide in 25 ml of dry methyl ethyl ketone was heated in a pressure bottle at 110° for 6 hr.[11] After cooling to room temperature, the solid was removed by filtration and the filtrate was concentrated to dryness. The residue was triturated with water and the solid **5a** which formed was collected, dried, and recrystallized from ethyl alcohol: yield 1 g (43.5%); mp 232–234°; $[\alpha]^{25}D$ +34.3° (*c* 1, DMF); mass spectrum *m/e* 461; nmr (DMSO) δ 1.25–1.62 (3, CH_3) and 3.39 (s, 3, $-OCH_3$).

Anal. Calcd for $C_{17}H_{20}NIO_6$: N, 3.04; I, 27.53. Found: N, 3.04; I, 27.62.

Methyl 2-Benzamido-2,6-dideoxy-6-iodo-3-*O*-[D-1-(methoxycarbonyl)ethyl]-β-D-glucopyranoside (6).—A solution of 300 mg (0.612 mmol) of **5a** and 33 mg (0.612 mmol) of sodium methoxide in 25 ml of dry methyl alcohol was left at room temperature overnight. The solution was made slightly acidic with glacial acetic acid and evaporated to dryness. The white solid residue was triturated with water, collected, and recrystallized from ethyl acetate. A 100-mg yield of **6** was obtained: mp 189–191°; mass spectrum *m/e* 493; nmr (DMSO) δ 2.75 and 2.84 (singlets, 3 each, 2 CH_3O–) and 1.03–1.10 (d, 3, CH_3); $[\alpha]^{25}D$ +16.4° (*c* 1, DMF).

Anal. Calcd for $C_{18}H_{24}INO_7$: C, 43.80; H, 492; N, 2.84; I, 25.70. Found: C, 43.72; H, 4.86; N, 2.69; I, 25.56.

Methyl-2-benzamido-2,6-dideoxy-3-*O*-(D-1-carboxyethyl)-D-glucopyranoside-4-lactone Methanolate (5b).—A solution of 6.9 g (1.48 mmol) of **5a** in 172 ml of methyl alcohol and 18 ml of triethylamine was hydrogenated with Raney nickel at 44 psi.[11] The reduction took 2 hr, after which time the catalyst was removed by filtration and the filtrate was evaporated to dryness. The solid residue was triturated with water, collected, and recrystallized from methanol, giving 3.2 g (62%) of **5b** as its methanolate: mp 199–200°; $[\alpha]^{25}D$ +15.7° (*c* 1, DMF); mass spectrum *m/e* 368.

Anal. Calcd for $C_{17}H_{21}NO_6 \cdot CH_3OH$: C, 58.85; H, 6.82; N, 3.82. Found: C, 58.84; H, 6.98; N, 3.90.

2-Amino-2,6-dideoxy-3-*O*-(D-1-carboxyethyl)-D-glucopyranose Hydrochloride (7).—The hydrolysis of **5b** was performed in the same manner as described for the preparation of **4**. A 2.2-g yield of crude product was obtained which, after recrystallization from acetone, gave 850 mg (53.5%) of **7**: mp 174–175°; $[\alpha]^{25}D$ +111.0° (*c* 1, DMF).

Anal. Calcd for $C_9H_{17}NO_6 \cdot HCl$: N, 5.14; Cl, 13.05. Found: N, 5.12; Cl, 13.26.

Registry No.—Amine (III) salt of **1a**, 23924-09-6; **1b**, 23912-19-8; **2b**, 23912-20-1; **2c**, 23912-21-2; **2d**, 23912-22-3; **2f**, 23924-03-0; **3b**, 23924-04-1; **4**, 23924-05-2; **5a**, 23924-06-3; **5b**, 23967-32-0; **6**, 23924-07-4; **7**, 23924-08-5.

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A Convenient Synthesis of Protected N-Methylamino Acid Derivatives

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Methylation of the amide nitrogen of selected N-benzyloxycarbonyl and N-*t*-butyloxycarbonylamino acids with methyl iodide and silver oxide in dimethylformamide gives the corresponding N-methylamino acid derivatives in excellent yield. An unprotected carboxyl group also is converted by methylation into the methyl ester. The methylation reaction was shown to occur without racemization of the amino acid. The methyl esters obtained were converted by saponification into the corresponding N-protected N-methylamino acids. The N-*t*-butyloxycarbonyl derivatives of cysteine and serine gave, upon methylation, unsaturated amino acid products.

N-Methylamino acids are constituents of several naturally occurring peptide and depsipeptide antibiotics.[1] Peptides that contain N-methylamino acids are also of interest in relation to studies of peptide conformations.[2] Suitable synthetic methods for the preparation of N-methylamino acids are, therefore, of importance pursuant to the synthesis of peptide antibiotics and of N-methylated peptides. We herein report a convenient one-step synthesis of N-monomethyl-α-amino acids suitably protected for further elaboration in peptide synthesis.

The method of choice for the preparation of optically pure N-methylamino acids involves a three-step sequence in which an N-benzylamino acid is methylated with formaldehyde–formic acid followed by reductive removal of the N-benzyl group.[3] The N-methylamino

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acid thus obtained must yet be converted to an appropriately protected derivative prior to use in peptide synthesis.

It was reported[4] recently, in connection with studies on the determination of amino acid sequences in peptides using mass spectrometry, that milligram quantities of N-acyl oligopeptides can be permethylated by treatment with methyl iodide and silver oxide in dimethylformamide. The above reaction also has been applied to the permethylation of peptides substituted with N-benzyloxycarbonyl or N-*t*-butyloxycarbonyl groups.[5] We report in this paper the application of the above methylation procedure on a preparative scale to the readily available and widely used N-benzyloxycarbonyl- and N-*t*-butyloxycarbonyl-L-amino acid derivatives of monoamino monocarboxylic acids. This reaction effects methylation of the amide nitrogen and affords in one step and in nearly quantitative yield the corresponding optically active N-methylamino acid derivatives (Tables I and II). An unprotected carboxyl group also undergoes methylation to give the corresponding methyl ester. The N-methylamino acid derivatives listed in Table I were obtained as oils that appeared to be homogeneous as shown by thin layer chromatography and nmr spectral data. Since N-methylamino acid derivatives generally show poor crystalline properties, the homogeneity of the products obtained is an important aspect of the method.

Table I

Methylation of N-Benzyloxycarbonyl- and N-*t*-Butyloxycarbonyl-L-amino Acids with Methyl Iodide and Silver Oxide in Dimethylformamide

Reactant	Product	Yield, %
Z-Ala-OH (**1**)[a]	Z-MeAla-OMe (**2**)	94
Z-Phe-OH (**3**)	Z-MePhe-OMe (**4**)	97
Z-Val-OBzlNO_2 (**5**)	Z-MeVal-OBzlNO_2 (**6**)	93
Boc-Ala-OH (**7**)	Boc-MeAla-OMe (**8**)	94
Boc-Ile-OH (**9**)	Boc-MeIle-OMe (**10**)	98
Boc-Val-OH (**11**)	Boc-MeVal-OMe (**12**)	94

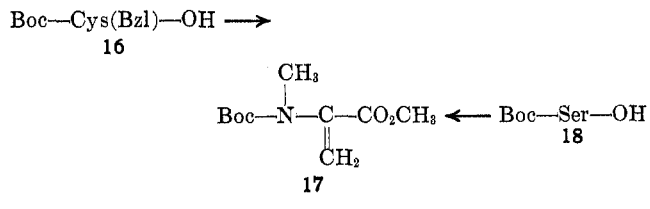
[a] Abbreviations used are those recommended by the IUPAC–IUB Commission on Biochemical Nomenclature, *J. Biol. Chem.*, **241**, 2491 (1966).

Spectral data obtained for the methylated products were consistent with the assigned structures. The infrared spectra lacked absorption due to amide NH or carboxyl OH in the region of 3200–3600 cm^{-1} indicative of complete methylation, while possessing two carbonyl bands assignable to ester and urethan functions. In the nmr spectra, a singlet at approximately τ 7.1 due to the N-methyl protons was observed in all cases. A singlet at τ 6.3 typical of an O-methyl group was present in the spectra of the methyl esters.

The N-methylamino acid derivatives were further characterized by conversion to and comparison with known compounds. Thus, **2** gave upon saponification N-benzyloxycarbonyl-N-methyl-L-alanine (**13**);[6] likewise, **4**, **6**, and **8**, upon removal of the protective groups, yielded N-methyl-L-phenylalanine, N-methyl-L-valine, and N-methyl-L-alanine trifluoroacetate, respectively. That no appreciable racemization had occurred upon methylation was established by comparison of the specific rotations of the above deprotected N-methylamino acids with reported rotations (Table II).

The N-benzyloxycarbonyl- and N-*t*-butyloxycarbonyl-N-methylamino acid methyl esters obtained were converted by mild saponification of the ester function to the corresponding optically pure N-protected amino acids. The nmr spectra of the resulting acids showed the disappearance of the singlet at approximately τ 6.3 due to the methyl ester protons, while the infrared spectra possessed absorption typical of carboxylic acids. Thus, N-benzyloxycarbonyl- and N-*t*-butyloxycarbonylamino acids can be converted by a two-step procedure of methylation and saponification to N-methylamino acid derivatives appropriately protected for direct use in peptide synthesis.[7]

The methylation reaction appears to be most applicable for the preparation of N-methylamino acid derivatives of monoamino monocarboxylic acids not containing other functional groups capable of undergoing methylation. Previous studies[5] have indicated various difficulties attendant with the permethylation of peptides containing arginine, aspartic acid, glutamic acid, methionine, serine, or threonine. In the present study, attempts to prepare N-methylamino acid derivatives of cysteine or serine were without success. Treatment of N-*t*-butyloxycarbonyl-*S*-benzyl-L-cysteine (**16**) or the corresponding L-serine derivative **18** yielded a mixture of products as shown by thin layer chromatography. The only ninhydrin-positive material present in the mixtures was shown to be the dehydroalanine derivative **17**. The ultraviolet spectrum of **17** had maximum absorption at 240 mμ consistent with that reported[8] for similar dehydroalanine derivatives. The nmr spectrum of **17** showed two one-proton singlets at τ 4.16 and 4.63 assignable to olefinic hydrogens, while absorption due to the S-benzyl group was not present. Hydrogenation[9] of **17** over platinum oxide yielded material shown to be chromatographically (tlc) and spectrally (ir, nmr) indistinguishable from methyl N-*t*-butyloxycarbonyl-N-methyl-L-alaninate (**8**). The formation of **17** in the methylation reaction can be rationalized by an elimination reaction of an intermediate sulfonium or oxonium salt.



The N-methylamino acids commonly found in peptide antibiotics are most often derived from monoamino monocarboxylic acids.[1] Methylation with methyl iodide–silver oxide, therefore, offers a convenient synthetic route to protected derivatives of the N-methylamino acids present in peptide antibiotics.

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TABLE II

SPECIFIC ROTATIONS OF N-METHYL-L-AMINO ACID DERIVATIVES

N-Methylamino acid ester	$[\alpha]^{a}D$, deg	N-Protected N-methylamino acid	$[\alpha]^{a}D$, deg	Deprotected N-methylamino acid	$[\alpha]^{a}D$, deg	Lit. $[\alpha]^{a}D$, deg
Z-MeAla-OMe (2)	−30	Z-MeAla-OH (13)	−31			−33.1[b]
Z-MePhe-OMe (4)	−77	Z-MePhe-OH (14)	−67	H-MePhe-OH	+48	+49.3[c]
Z-MeVal-OBzlNO_2 (6)	−59			H-MeVal-OH	+32	+33[c]
Boc-MeAla-OMe (8)	−40	Boc-MeAla-OH (15)	−29	TFA$^-H_2^+$-MeAla-OH	+5	+5[d]

[a] See Experimental Section for conditions of temperature, concentration, and solvent. [b] Reference 6. [c] Reference 3. [d] Determined from an authentic sample; see Experimental Section.

Experimental Section

Melting points were determined on a Thomas–Hoover capillary apparatus and are uncorrected. Infrared spectra were obtained with a Beckman IR-8 spectrophotometer. The nmr spectra were recorded at 60 MHz on a Varian A-60 spectrometer. Mass spectra were measured on a Hitachi Perkin-Elmer RMU-6E mass spectrometer. Solvents were removed *in vacuo* on a Buchler rotary evaporator at bath temperatures below 40°.

Thin layer chromatographic data were obtained upon Brinkmann silica gel precoated plates in the following ascending solvent systems: R_{fA}, ligroin (bp 60–90°)-ethyl acetate (15:2); R_{fB}, chloroform–acetic acid (95:5); and R_{fC}, chloroform–methanol–acetic acid (85:10:5). Spots were detected with ninhydrin spray reagent after the developed plate had been treated with hydrochloric acid vapors.[10] To develop spots due to N-methylamino acids, it was necessary to heat the plate at 110° for 2–4 min. Where applicable, the spots were also viewed under ultraviolet light on silica gel F_{254} plates.

The silver oxide used was of reagent grade purchased from Matheson Coleman and Bell. The dimethylformamide was reagent grade and was distilled from calcium oxide. The N-benzyloxycarbonyl- and N-*t*-butyloxycarbonylamino acids employed were purchased commercially.

General Procedure for Methylation of N-Protected Amino Acid Derivatives.—The N-benzyloxycarbonyl- or N-*t*-butyloxycarbonylamino acid was dissolved in anhydrous dimethylformamide. To the resulting solution was added methyl iodide (four- to eightfold molar excess) and silver oxide (three- to fourfold molar excess.) The reaction mixture was stirred magnetically at room temperature for 5–8 hr in case of the N-benzyloxycarbonyl derivatives, while for the N-*t*-butyloxycarbonylamino acids the reaction mixture was stirred at 45° for several hours. The mixture was filtered and the solid washed with a small volume of dimethylformamide. To the filtrate was added approximately a fourfold volume of chloroform. The chloroform phase, in which a precipitate had formed, was washed twice with 5% aqueous potassium cyanide, several times with water, and was dried over magnesium sulfate. The drying agent was removed by filtration and the solvent evaporated *in vacuo*. The last traces of dimethylformamide usually present were removed *in vacuo* with an oil vacuum pump at a bath temperature below 40°. The methylated products were obtained in good yield as chromatographically homogeneous oils.

Methyl N-Benzyloxycarbonyl-N-methyl-L-alaninate (2).—A solution of 3 g (13.5 mmol) of **1** in 40 ml of anhydrous dimethylformamide was stirred at room temperature with 7 ml (108 mmol) of methyl iodide and 12.5 g (54 mmol) of silver oxide for 8 hr. There was obtained 3.2 g (94%) of a clear oil: tlc R_{fA} 0.29, R_{fB} 0.74; ir (film) no NH or OH absorption at 3600–3200, 1725, 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 2.66 (s, 5 H, phenyl), 4.85 (s, 2 H, benzyl), 5.25 (s, 1 H, α proton), 6.34 (s, 3 H, methyl ester), 7.12 (s, 3 H, N-methyl), 8.61 (d, J = 7.5 Hz, 3 H, α-methyl protons). An analytical sample was prepared by short-path distillation, bp 110–113° (0.1 mm), $[\alpha]^{24}D$ −30° (*c* 1.0, AcOH).

Anal. Calcd for $C_{13}H_{17}NO_4$ (251.2): C, 62.2; H, 6.82; N, 5.58. Found: C, 61.9; H, 7.01; N, 5.43.

Treatment of 0.237 g (1 mmol) of methyl N-benzyloxycarbonyl-L-alaninate as above gave 0.20 g (81%) of an oil indistinguishable chromatographically and spectrally from **2**.

Methyl N-Benzyloxycarbonyl-N-methyl-L-phenylalaninate (4).—A solution of **3** (2.0 g, 6.7 mmol) in 30 ml of anhydrous dimethylformamide was stirred at room temperature with 1.7 ml (27.6 mmol) of methyl iodide and 4.66 g (20.1 mmol) of silver oxide for 8 hr. A pale yellow oil (2.04 g, 97% yield) was obtained: tlc R_{fA} 0.33, R_{fB} 0.64; ir (film) no absorption 3200–3600, 1730, and 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 2.75 (m, 10 H, phenyl groups), 4.92 (s, 2 H, O-benzyl), 5.1 (m, 1 H, α hydrogen), 6.30 (s, 3 H, methyl ester), 6.76 (d, 2 H, α-benzyl), 7.18 (s, 3 H, N-methyl); $[\alpha]^{24}D$ −77° (*c* 1.6, EtOH). An analytical sample was prepared by chromatography of the oil on neutral alumina and elution with hexane–ethyl acetate (98:2).

Anal. Calcd for $C_{19}H_{21}NO_4$ (327.4): C, 69.8; H, 6.48; N, 4.28. Found: C, 69.8; H, 6.74; N, 4.23.

***p*-Nitrobenzyl-N-benzyloxycarbonyl-L-valinate (5).**—This compound was prepared according to the procedure of Schwarz and Arakawa.[11] A solution of N-benzyloxycarbonyl-L-valine (5.02 g, 20 mmol), *p*-nitrobenzyl bromide (6.48 g, 30 mmol), and triethylamine (4.2 ml, 30 mmol) in 150 ml of ethyl acetate was heated at reflux for 16 hr. The solid was filtered and to the hot filtrate was added 2.5 ml of methanol. The cooled organic phase was washed once with cold water, three times with 1 *N* hydrochloric acid, once with water, three times with 1 *M* sodium bicarbonate, and three times with saturated sodium chloride, and dried over magnesium sulfate. Evaporation of the solvent *in vacuo* yielded 6.86 g (89%) of pale yellow crystals, mp 103–105°. Recrystallization from ethyl acetate–ligroin (bp 60–90°) gave white crystals: mp 104.5–105.5°; ir ($CHCl_3$) 3420 (N—H), 1725 (C=O), 1520 and 1350 cm^{-1} (NO_2); nmr ($DCCl_3$) τ 2.26 (center of AB pattern, 4 H, nitro phenyl), 2.77 (s, 5 H, phenyl), 4.84 (s, 2 H, benzyl), 4.97 (s, 2 H, benzyl), 5.73 (m, 1 H, α hydrogen), 7.90 (m, 1 H, methine hydrogen), 9.14 (pair d, 6 H, nonequivalent isopropyl methyl groups).

Anal. Calcd for $C_{20}H_{22}N_2O_6$ (386.4): C, 62.2; H, 5.75; N, 7.25. Found: C, 62.6; H, 5.76; N, 7.46.

***p*-Nitrobenzyl N-Benzyloxycarbonyl-N-methyl-L-valinate (6).**—One gram (2.6 mmol) of **5** in 8 ml of anhydrous dimethylformamide was treated with 4 ml (64.8 mmol) of methyl iodide and 0.6 g (2.6 mmol) of silver oxide for 5 hr at room temperature. If the reaction was carried out on a larger scale or allowed to proceed for longer periods of time, multiple spots were observed upon thin layer chromatography. There was obtained from the reaction 0.97 g (93%) of a light yellow oil: tlc R_{fA} 0.23, R_{fB} 0.90; ir (CCl_4) no absorption 3600–3200, 1730 and 1700 (C=O), 1530 and 1350 cm^{-1} (NO_2); nmr ($DCCl_3$) τ 2.25 (center of AB pattern, nitrophenyl, 4 H), 2.73 (s, 5 H, phenyl), 4.82 (s) and 4.87 (s) (total 4 H, benzyl groups), 5.53 (m, 1 H, α hydrogen), 7.10 (s, 3 H, N-methyl), 7.78 (m, 1 H, isopropyl methine), 9.05 (pair of d, 6 H, nonequivalent isopropyl protons); $[\alpha]^{25}D$ −59° (*c* 1.0, AcOH); parent peak *m/e* 400, 100% *m/e* 91. An analytical sample was prepared by chromatography of the oil on neutral alumina and elution with hexane-ethyl acetate (3:1).

Anal. Calcd for $C_{21}H_{24}N_2O_6$ (400.4): C, 63.0; H, 6.05; N, 6.98. Found: C, 62.7; H, 6.31; N, 6.98.

Methyl N-*t*-Butyloxycarbonyl-N-methyl-L-alaninate (8).—A mixture of **7** (1.0 g, 5.3 mmol), methyl iodide (2.6 ml, 42.4 mmol), and silver oxide (4.9 g, 21.2 mmol) in 25 ml of anhydrous dimethylformamide was stirred at 45° for 5 hr, followed by continued stirring at room temperature for 14 hr. Following workup of the reaction mixture, there was obtained 1.08 g (94%) of a clear oil: tlc R_{fA} 0.39, R_{fB} 0.71; ir (CCl_4) no OH or NH absorption 3600–3200, 1735 and 1695 cm^{-1} (C=O); nmr ($DCCl_3$) τ 5.35 (m, 1 H, α hydrogen), 6.29 (s, 3 H, methyl ester), 7.17 (s, 3 H, N-methyl), 8.56 (s, 9 H, *t*-butyl), 8.63 (d, 3 H, α-methyl group with one peak of doublet superimposed on peak due to *t*-butyl group); $[\alpha]^{26}D$ −40° (*c* 2.1, ethanol). An analytical

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(11) H. Schwarz and K. Arakawa, *J. Amer. Chem. Soc.*, **81**, 5691 (1959).

sample was prepared by short-path distillation, bp 105–108° (20 mm).

Anal. Calcd for $C_{10}H_{19}NO_4$ (217.2): C, 55.2; H, 8.82; N, 6.45. Found: C, 55.0; H, 8.70; N, 6.55.

Methyl N-*t*-Butyloxycarbonyl-N-methyl-L-isoleucinate (10).—A mixture of **9** (1.0 g, 4.33 mmol), methyl iodide (1.1 ml, 17.3 mmol), and silver oxide (3.04 g 13.0 mmol) in 20 ml of anhydrous dimethylformamide was stirred at 45° for 18 hr. Work-up of the reaction mixture yielded 1.10 g (98%) of clear liquid: tlc R_{fA} 0.70, R_{fB} 0.83; ir (film) no OH or NH absorption 3600–3200, 1730 and 1685 cm^{-1} (C=O); nmr ($DCCl_3$) τ 5.58 (m, 1 H, α hydrogen), 6.27 (s, 3 H, methyl ester), 7.16 (s, 3 H, N-methyl), 8.0 (brd m, 1 H, methine), 8.55 (s, 9 H, *t*-butyl), 9.0–9.2 (m, 8 H, isoleucyl group protons); parent peak *m/e* 259; $[\alpha]^{29}D$ −86° (*c* 1.94, EtOH). An analytical sample was prepared by short-path distillation, bp 82° (0.1 mm).

Anal. Calcd for $C_{13}H_{25}NO_4$ (259.3): C, 60.2; H, 9.74; N, 5.41. Found: C, 60.3; H, 9.78; N, 5.75.

Methyl N-*t*-Butyloxycarbonyl-N-methyl-L-valinate (12).—A solution of **11** (3.0 g, 13.8 mmol) in 40 ml of anhydrous dimethylformamide was stirred with 16.0 g (113 mmol) of methyl iodide and 12.3 g (53 mmol) of silver oxide at 45° for 16 hr to yield 3.19 g (94%) of **12** as a clear liquid: tlc R_{fA} 0.49, R_{fB} 0.73; ir (film) no absorption 3200–3600, 1730 and 1690 cm^{-1} (C=O); nmr ($DCCl_3$) τ 5.75 (m, 1 H, α hydrogen), 6.30 (s, 3 H, methyl ester), 7.17 (s, 3 H, N-methyl), 7.80 (m, 1 H, methine), 8.55 (s, 9 H, *t*-butyl), 9.07 (pair d, 6 H, nonequivalent isopropyl methyl groups); $[\alpha]^{24}D$ −51° (*c* 2.1, EtOH). An analytical sample was prepared by short-path distillation, bp 77° (0.3 mm).

Anal. Calcd for $C_{12}H_{23}NO_4$ (245.3): C, 58.8; H, 9.45; N, 5.71. Found: C, 58.7; H, 9.54; N, 5.95.

N-Benzyloxycarbonyl-N-Methyl-L-alanine (13).—A solution of **2** (1.5 g, 6.0 mmol) and 6.2 ml of 1 *N* sodium hydroxide in 20 ml of 95% ethanol was allowed to stand at room temperature for 1 hr. The major portion of the solvent was evaporated *in vacuo*, after which 15 ml of water was added. The resulting solution was cooled and acidified to pH 3 with 1 *N* hydrochloric acid. The aqueous phase was extracted three times with ethyl acetate, following which the organic phase was washed several times with water and dried over magnesium sulfate. The drying agent was filtered and the solvent removed *in vacuo* to yield 1.13 g (80%) of an oil that slowly solidified upon standing, mp 59.5–64.0°. Recrystallization from benzene–hexane gave white crystals melting at 62.0–64.0° (lit.[6] 62.0–64.5°); tlc R_{fB} 0.45, R_{fC} 0.68; nmr ($DCCl_3$) τ 2.67 (s, 5 H, phenyl), 4.84 (s, 2 H, benzyl), 5.2 (m, 1 H α-hydrogen), 7.08 (s, 3 H, N-methyl), 8.58 (d, J = 7.5 Hz, 3 H, α-methyl protons); $[\alpha]^{28}D$ −31° (*c* 2, AcOH) {lit.[6] $[\alpha]^{28}D$ −33.1 (*c* 2, AcOH)}.

N-Benzyloxycarbonyl-N-methyl-L-phenylalanine (14).—A solution of **4** (2.92 g, 8.9 mmol) and 10.0 ml (10 mmol) of 1 *N* sodium hydroxide in 35 ml of ethanol (room temperature, 2.5 hr) was saponified as described above for **13** to yield 2.20 g (79%) of an oil that slowly solidified upon standing, mp 65–70°. Three recrystallizations from ethyl acetate–hexane gave crystals melting at 67–71°: tlc R_{fB} 0.45, R_{fC} 0.69; ir (film) 3400–2500 (carboxyl OH), 1700 cm^{-1} (C=O); nmr ($DCCl_3$) τ 0.10 (s, 1 H, carboxyl hydrogen), 2.75 and 2.80 (2 s, 10 H, phenyl groups), 4.92 (s, 2 H, O-benzyl), 5.1 (m, 1 H, α hydrogen), 6.75 (m, 2 H, α-benzyl), 7.21 (s, 3 H, N-methyl); $[\alpha]^{28}D$ −67° (*c* 1.8, EtOH).

Anal. Calcd for $C_{18}H_{19}NO_4$ (313.3): C, 69.1; H, 6.11; N, 4.47. Found: C, 69.2; H, 6.04; N, 4.38.

N-*t*-Butyloxycarbonyl-N-methyl-L-alanine (15).—A solution of **8** (0.60 g, 2.77 mmol) and 3 ml of 1 *N* sodium hydroxide in 15 ml of ethanol was saponified as described for **13** to give 0.37 g (66%) of crystals. Recrystallization from ligroin gave material melting at 89–91° (lit.[12] 89°): tlc R_{fB} 0.47, R_{fC} 0.71, ir (film) 3500–2500 (carboxyl OH), 1725, 1650 (C=O); nmr ($DCCl_3$) τ 5.34 (m, 1 H, α hydrogen), 7.15 (s, 3 H, N-methyl), 8.55 (s, 9 H, *t*-butyl), 8.60 (d, 3 H, α-methyl); $[\alpha]^{26}D$ −29° (*c* 1.0, EtOH).

Anal. Calcd for $C_9H_{17}NO_4$ (203.2): C, 53.3; H, 8.42; N, 6.90. Found: C, 53.2; H, 8.67; N, 6.82.

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Conversion of *p*-Nitrobenzyl N-Benzyloxycarbonyl-N-methyl-L-valinate (6) to N-Methyl-L-valine.—The hydrogenolysis of **6** was carried out following the procedure described by Schwarz and Arakawa.[11] One gram (2.5 mmol) of **6** was dissolved in 20 ml of 1:1 ethyl acetate–methanol. To this solution was added 4.0 ml of 1 *N* hydrochloric acid and 0.30 g of 10% palladium on charcoal. The reaction mixture was hydrogenated at 15 psi of hydrogen for 2 hr. The catalyst was filtered and washed with methanol. To the filtrate was added 5.7 ml of triethylamine and the solvent was removed *in vacuo* to yield a yellow oil. The oil was dissolved in 5 ml of hot water followed by the addition of 75 ml of ethanol. The white crystals, which formed upon cooling, were collected by filtration and allowed to air dry (0.17 g, 51%). The solid material obtained was chromatographically indistinguishable from an authentic sample of N-methyl-L-valine: $[\alpha]^{30}D$ +32° (*c* 1.7, 6 *N* HCl) {lit.[3] $[\alpha]D$ +33° (*c* 1, 6 *N* HCl)}.

Conversion of N-Benzyloxycarbonyl-N-methyl-L-phenylalanine (12) to N-Methyl-L-phenylalanine.—A solution of **12** (0.45 g, 1.43 mmol) in 30 ml of 1:1 ethyl acetate–methanol containing 2.2 ml of 1 *N* hydrochloric acid and 0.17 g of 10% palladium on charcoal was hydrogenated at 18 psi of hydrogen for 2 hr. Treatment as described above for the hydrogenolysis of **6** gave 0.23 g (90%) of a white solid. This material was recrystallized once from water: mp 255–260° dec (lit.[3] 260° dec); $[\alpha]^{26}D$ +48° (*c* 1.0, 1 *N* NaOH) {lit.[3] $[\alpha]D$ +49.3° (*c* 1.0, 1 *N* NaOH)}.

Conversion of N-*t*-Butyloxycarbonyl-N-methyl-L-alanine (15) to N-Methyl-L-alanine Trifluoroacetate.—A solution of **13** (107 mg) was allowed to stand at room temperature for 2 hr in 10 ml of trifluoroacetic acid. Removal of the solvent *in vacuo* yielded a clear oil. The oil was dissolved in 3 ml of ethyl acetate followed by the addition of 3 ml of ligroin. White crystals formed within minutes upon standing. After cooling, the crystals were filtered, washed with 1:1 ethyl acetate–ligroin, and air-dried. There was obtained 140 mg (120%) of product, mp 135–136.5°, $[\alpha]^{28}D$ +5° (*c* 2, EtOH).

Treatment of N-methyl-L-alanine (Cyclo Chemical) with trifluoroacetic acid as above gave the same compound: mp 135–136.5°; mmp 135–136°; $[\alpha]^{28}D$ +5° (*c* 2, EtOH).

Anal. Calcd for $C_6H_{10}F_3NO_4$ (217.1): C, 33.2; H, 4.61; N, 6.46. Found: C, 33.3; H, 4.74; N, 6.58.

Methylation of *S*-Benzyl-N-*t*-butyloxycarbonyl-L-cysteine.—The cysteine derivative **16** (0.50 g, 1.6 mmol) was treated with 1.1 ml (17.3 mmol) of methyl iodide and 2.0 g (8.95 mmol) of silver oxide at 27° for 6 hr as described above in the general procedure to yield 0.36 g of a clear oil. Tlc showed one ninhydrin-positive spot, R_{fA} 0.35; however, four spots were visible under ultraviolet light. Short-path distillation gave 0.18 g of a clear oil that was shown by tlc to still contain small amounts of two materials having higher R_f values than the major ninhydrin-sensitive material: uv max (cyclohexane) 240 mμ; nmr ($DCCl_3$) τ 2.61 (weak peak due to impurity), 4.16 (s, 1 H, vinyl proton), 4.63 (s, 1 H, vinyl proton), 6.21 (s, 3 H, methyl ester), 6.87 (s, 3 H, N-methyl), 8.58, (s, 9 H, *t*-butyl); $[\alpha]^{25}D$ 0° (*c* 1, EtOH). Hydrogenation of **17** (120 mg) at 20 psi of hydrogen over platinum oxide (65 mg) at room temperature for 4.5 hr gave **8** as established by comparison of tlc, ir, and nmr data.

N-*t*-Butyloxycarbonyl-L-serine (**18**), when treated with methyl iodide–silver oxide in dimethylformamide, yielded results similar to those obtained above for the corresponding cysteine derivative **16**.

Registry No.—**2**, 24164-72-5; **4**, 24164-73-6; **5**, 5276-76-6; **6**, 24164-75-8; **8**, 24164-04-3; **10**, 24164-05-4; **12**, 24164-06-5; **13**, 21691-41-8; **14**, 2899-07-2; **15**, 16948-16-6; N-methyl-L-alaninetrifluoroacetate, 24164-10-1.

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