Methallylamine.—Hydrolysis of the amide obtained by both methods A and B yielded methallylamine which was identified by the preparation of a picrate, m.p. 204–206° (lit. m.p. 202.5–204.5°,[3] 202–206°[9]), and a phenylthiourea derivative, m.p. 76–77° (lit.[3] m.p. 78–79°), and by benzoylation to N-methallylbenzamide, m.p. 66–67° (lit.[3] m.p. 69.5–70.5°).

2-Ethyl-5,5-dimethyl-2-oxazoline (III).—An 18.5-g. portion of amide product obtained by method B, b.p. 130–135° (20 mm.), was added to 25 ml. of concentrated H_2SO_4 with stirring and cooling (temperature kept at 30–35°) in 15 min. The mixture was then poured onto 200 g. of crushed ice. Sodium hydroxide (40 g.) and water (50 ml.) were added (ice bath cooling), and the mixture was extracted with three 50-ml. portions of ether. Distillation of the dried extract gave 9.0 g. of 2-ethyl-5,5-dimethyl-2-oxazoline, b.p. 139–144° (lit.[3] b.p. 141°).

Anal. Calcd. for $C_7H_{13}NO$: N, 11.01; neut. equiv., 127.2. Found: N, 11.05; neut. equiv., 129.0.

A picrate of this material, m.p. 144–146° (lit.[3] m.p. 147–149°), was shown to differ from the picrate, m.p. 151–154°, of 2-ethyl-4,4-dimethyl-2-oxazoline by mixture melting point (123–128°).

Pyrolysis of 2-Phenyl-4,4-dimethyl-2-oxazoline. N-Methallylbenzamide.—N-Methallylbenzamide, b.p. 113–117° (0.05 mm.), was obtained in a 21% yield (based on oxazoline charged) by pyrolysis of 2-phenyl-4,4-dimethyl-2-oxazoline at 597° using method A.

Pyrolysis of the oxazoline at 559° by method B but at reduced pressure (50 mm.) gave a 79% yield of amide (28% oxazoline conversion), b.p. 136–142° (1 mm.), in 26.5 hr. The reflux temperature rose from 152 to 159.5°. Analysis of the product by gas chromatography indicated a purity of 93.5%.

Anal. Calcd. for N-methallylbenzamide, $C_{11}H_{13}NO$: N, 8.00; iodine no., 144.8. Found: N, 8.09; iodine no., 143.

Similarly prepared material, b.p. 141–143° (1 mm.), was recrystallized from petroleum ether to m.p. 68–69° (lit.[3] m.p. 69.5–70.5°). A mixture melting point with an authentic sample was not depressed.

Pyrolysis of 2,4-Dimethyl-2-oxazoline. N-Allylacetamide.—N-Allylacetamide, b.p. 102–105° (10 mm.), lit.[10] b.p. 113–116° (15 mm.), was obtained in a 44% yield (46% oxazoline conversion by pyrolysis of 2,4-dimethyl-2-oxazoline at 586° using method A.

Anal. Calcd. for N-allylacetamide, C_5H_9NO: N, 14.13; iodine no., 256. Found: N, 14.80; iodine no., 236.

The structure of this impure product was also supported by an infrared spectrum [bands at 3.06 (NH) and at 6.08 μ (C=O)] and by a n.m.r. spectrum [δ 1.97 (CH_3CO), 3.75 (=C-CH_2-N-), 5 (=CH_2), 5.7 (=CH-), and 7.5 (-NH-)]. A slight amount of impurity was also indicated by the presence of small extraneous peaks throughout the n.m.r. spectrum.[11]

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A New Synthesis of α-L-Aspartyl-L-leucine[1]

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The major obstacle to the synthesis of α-aspartyl peptides is the presence of two nonequivalent carboxyl groups. One way of circumventing this difficulty is to utilize a precursor which can be converted under mild conditions to a β-carboxylic acid after formation of the α-peptide bond. The conversion of L-allylglycine (L-2-amino-4-pentenoic acid) to α-aspartyl peptides would afford such a route. As an illustration, α-L-aspartyl-L-leucine has been prepared from *p*-nitrocarbobenzoxy-L-allylglycyl-L-leucine by oxidation with periodate in the presence of catalytic amounts of permanganate.[2] The compound thus prepared is chromatographically pure and is indistinguishable from the product obtained by the condensation of β-benzyl carbobenzoxy-L-aspartate and L-leucine benzyl ester followed by hydrogenolysis.[3]

Coupling reactions with carbobenzoxy- or *p*-nitrocarbobenzoxy-L-allylglycine proceed smoothly either with dicyclohexylcarbodiimide or ethyl chloroformate. The original procedure of Lemieux and Rudloff[2] for the oxidation of unsaturated fatty acids was modified to permit work at higher concentrations. The course of the oxidation can be followed quantitatively by iodimetric titration or qualitatively by the pH rise. The most favorable pH range is between 7 and 9. The rate of oxidation is rapid at 20° in solutions that are 0.1 *M*, 0.025 *M*, and 0.001 *M* with respect to periodate, substrate, and permanganate, respectively. The aspartyl derivatives were isolated either by extraction from the acidified solutions with ethyl acetate or by precipitation from the concentrated aqueous solution after reduction of the excess oxidants with sodium metabisulfite.[4] Yields between 60 and 95% of the theoretical were obtained.

Although the applicability of this approach to other α-aspartyl derivatives has not been studied, certain limitations are inherent in this procedure. Thus, appropriate protective groups are necessary for tyrosine, serine, and threonine. For example, it was found that N-carbobenzoxy-L-tyrosine reacted with permanganate but uptake of oxidant was drastically reduced with O-acetyl-N-carbobenzoxy-L-tyrosine under the conditions used for the oxidation of allylglycine derivatives. However, the carbobenzoxy derivatives of tryptophan, methionine, and cysteine compete with the olefin for oxidant, and peptides containing these amino acids cannot be synthesized directly by the procedure described above.

Experimental[5]

L-Allylglycine was prepared from N-acetyl-DL-allylglycine[6] by the use of hog kidney acylase.[7]

***p*-Nitrocarbobenzoxy-L-allylglycine.**—To 3.8 g. of L-allylglycine in 7.7 ml. of 4 *N* sodium hydroxide at 0° was added with stirring in four portions at 20-min. intervals 8.1 g. of *p*-nitrocarbobenzoxy chloride in 21 ml. of 1,4-dioxane and 10.3 ml. of 4 *N* sodium hydroxide. Stirring was continued for 4 hr. at 0°. The mixture was filtered, the precipitate was discarded, the filtrate was acidified with concentrated hydrochloric acid, and the oil was extracted with ethyl acetate. After washing with water, drying with magnesium sulfate, and evaporating the solvent, the extracts yielded an oil that crystallized from 25 ml. of benzene. After two recrystallizations from benzene, the yield was 6.0 g. (68%), m.p. 81–83°, $[\alpha]^{25}D$ +4.5° (*c* 3.5, dimethyl formamide).

Anal. Calcd. for $C_{18}H_{14}N_2O_6$: C, 53.06; H, 4.80; N, 9.52. Found: C, 53.00; H, 4.39; N, 9.82.

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p-Nitrocarbobenzoxy-L-allylglycyl-L-leucine Benzyl Ester.—To a solution of 1.176 g. (4 mmoles) of *p*-nitrocarbobenzoxy-L-allylglycine, 1.892 g. of L-leucine benzyl ester *p*-tosylate,[8] and 0.35 ml. of triethylamine in 40 ml. methylene chloride was added 0.940 g. of dicyclohexylcarbodiimide. The mixture was shaken overnight at room temperature; 0.5 ml. of acetic acid was added. The solvent was evaporated from the filtered solutions and the residue taken up in 100 ml. of ethyl acetate. The extract was washed with 0.5 *N* hydrochloric acid, water, saturated sodium hydrogen carbonate, and water. Concentration to 20 ml. yielded 1.57 g. (79%) of crude product, m.p. 140–142°. Recrystallization from methylene chloride and ligroin yielded 1.34 g., m.p. 146–148°.

Anal. Calcd. for $C_{26}H_{31}N_3O_7$: C, 62.76; H, 6.28; N, 8.45. Found: C, 62.84; H, 6.43; N, 8.98.

p-Nitrocarbobenzoxy-L-allylglycyl-L-leucine.—This compound could be prepared either by saponification of the benzyl ester (74% yield, m.p. 70–73°) or by direct coupling. To a solution of 1.176 g. of *p*-nitrocarbobenzoxy-L-allylglycine and 0.55 ml. of triethylamine in 12 ml. of tetrahydrofuran at −5° was added 0.38 ml. of ethylchloroformate. After 25 min., 576 mg. of L-leucine in 2.2 ml. of 2 *N* sodium hydroxide was added; the mixture was held at room temperature overnight. After evaporation of the solvent and addition of 15 ml. of water, the solution was extracted with ethyl acetate and the extract was discarded. The aqueous portion was acidified and extracted with ethyl acetate, the extract was washed with water and dried over magnesium sulfate, and the solvent was evaporated. After two crystallizations from toluene, 0.96 g. (59%) of product was obtained, m.p. 69–73°.

Anal. Calcd. for $C_{19}H_{25}N_3O_7$: C, 56.01; H, 6.19; N, 10.31; neut. equiv., 407. Found: C, 56.28; H, 6.21; N, 10.55; neut. equiv., 410.

Oxidation Procedure.—To 18 ml. of 0.115 *M* sodium metaperiodate at 20° was added 0.5 mmole of olefin; the pH was adjusted to 7.5 with 0.5 *M* sodium carbonate. The addition of 2 ml. of 0.01 *M* potassium permanganate initiates the oxidation. Usually, the reaction was stopped after 1 hr. by acidification to pH 2. In some experiments, the pH of the mixture was readjusted to pH 7.5 after the first hour and a second increment of 0.01 *M* potassium permanganate was added. However, the effect of this treatment on the yields of oxidation products was slight.

The aspartic acid derivatives have been isolated either by extraction with ethyl acetate or by crystallization from the concentrated reaction mixture. For the latter procedure, the cooled reaction mixture was titrated with 1 *M* sodium metabisulfite until a colorless solution was obtained, excess acid was destroyed with solid sodium hydrogen carbonate, the solution was concentrated under reduced pressure, and the pH was readjusted to pH 2. Storage of the mixture overnight at 4° yielded crystalline product.

Oxidation of 0.5 mmole of carbobenzoxy-L-allylglycine[6] gave carbobenzoxy-L-aspartic acid in 78% yield when extracted into ethyl acetate while *p*-nitrocarbobenzoxy-L-allylglycine was converted to *p*-nitrocarbobenzoxy-L-aspartic acid in 95% yield when isolated from the aqueous phase after sodium metabisulfite treatment.

Conversion of *p*-Nitrocarbobenzoxy-L-allylglycyl-L-leucine to α-L-Aspartyl-L-leucine.—The acidified oxidation mixture from 407 mg. of *p*-nitrocarbobenzoxy-L-allylglycyl-L-leucine was extracted twice with 30-ml. portions of ethyl acetate. The combined extracts were washed with water and dried over magnesium sulfate; the solvent was evaporated at reduced pressure. The residue, which was noncrystalline, was dissolved in 5 ml. of acetic acid and hydrogenated at room temperature and 1 atm. in the presence of 50 mg. of palladium black for 2 hr. Filtration, evaporation of most of the acetic acid, and addition of ether yielded 158 mg. (64%) of crystalline α-L-aspartyl-L-leucine, recrystallized from aqueous acetone for analysis.

Anal. Calcd. for $C_{10}H_{18}N_2O_5$: N, 11.38; neut. equiv., 246. Found: N, 11.44; neut. equiv. (titrated to pH 6.5), 251.

The material prepared by the above procedure and α-L-aspartyl-L-leucine prepared by the method of Bryant, *et al.*,[3] were indistinguishable; their infrared spectra as potassium bromide pellets were completely superimposable; each gave only one ninhydrin-positive spot after chromatography on Whatman No. I paper in *n*-butanol–acetic acid–water, 4:1:5 (v./v.), R_f 0.59 (Bryant, *et al.*,[3] reported R_f 0.60); $[\alpha]^{25}D$ −9.8° (*c* 3.3, 0.1 *N* hydrochloric acid) [Bryant, *et al.*,[3] reported $[\alpha]^{26}D$ −9.7° (*c* 3.42, 0.1 *N* hydrochloric acid)].

Quaternization of Aziridines. Evidence for the Monomeric State of Products[1]

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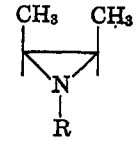
In the synthesis of a series of β-substituted amines, quaternary aziridinium salts were considered as potentially convenient alkylating agents. Protonated aziridines of varying stability have been isolated and described,[3–5] but there is no comparable description of exhaustively alkylated species prepared directly from aziridines. The exceptional reactivity of the quaternary salts toward nucleophiles has virtually restricted salt preparation to those exceptional instances in which the anion and solvent have low nucleophilicity,[6] the carbon skeleton has special steric features,[7,8] or (in one instance) a stable complex forms.[9] Quite recently, however, Bottini and VanEtten investigated the quaternization of *cis*- and *trans*-1,2-dimethyl-3-isopropylaziridine and demonstrated the formation of stable monomeric iodides.[10]

When *cis*- or *trans*-1,2,3-trimethylaziridine (**1a**) was treated with methyl iodide, a white crystalline solid formed rapidly. The product was found to de-



1a, R = CH_3
b, R = CH_3CH_2

compose readily on attempted recrystallization. Similar observations were made with isomers of 1-ethyl-2,3-dimethylaziridine (**1b**). If an analogy were made with the hydrochlorides of aziridines, it could not be assumed that the materials were monomeric species, for these protonated compounds polymerized vigorously at room temperature.[3,5] The instability of the quaternary salts to procedures used for crystallization, however, indicated a structural feature other than an unstrained, quaternized nitrogen atom of the piperazine type **4**. Such piperazinium salt formation has been observed[4,11] in the spontaneous dimerization of nitrogen mustards.

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