Hydrogen atoms of the methyl groups have not been located nor computed. R factors as well as residuals in final difference maps are given in Table IV. The only notable residuals are in the region of disorder of compound (*E*)-**6m**.

Supplementary Material Available: Tables of bond lengths and bond angles, coordinates, and anisotropic thermal parameters (20 pages). Ordering information is given on any current masthead page.

Synthesis of (*E*)- and (*Z*)-Cyclopropyl-3-chloroalanine

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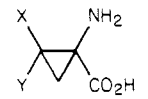
Both stereoisomers of cyclopropyl-3-chloroalanine (1) were synthesized by diazomethane cyclopropanation of the appropriate oxazolones (2). X-ray crystallographic analysis elucidated the configurations of 1 and gave some insight into its possible conformational preferences.

In pursuing our interest in cyclopropyl amino acids, we prepared the β-halo compound **1**. Since the addition of

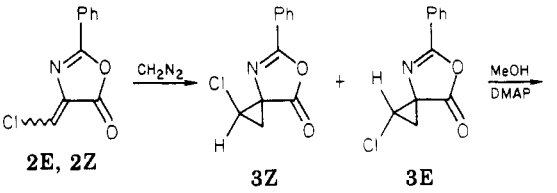


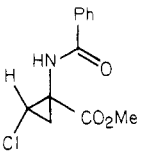
1E, X = H; Y = Cl
1Z, X = Cl; Y = H

diazomethane to unsaturated oxazolones is well-known[1] and since the requisite chloro compound **2** had been reported,[2] we prepared and studied its reaction with diazomethane. The configuration of **2** as reported in 1946 was unknown, and when the synthetic sequence (Scheme I) was carried out, only one isomer of **2** appeared to be produced, as determined by ^{1}H NMR and TLC analyses. However, when **2** was treated with CH_2N_2, a 1:11 mixture of isomeric cyclopropanes (**3**) was isolated in 75% yield. The predominant isomer of **3** was converted to the corresponding benzoyl methyl ester **4**, and X-ray crystallographic analyses showed it to be the *E* isomer. Assuming no isomerization during cyclopropanation or oxazolone ring opening, this indicated that the *E* isomer of the unsaturated oxazolone **2** also predominated. When the crude oxazolone **2E** was irradiated (3100 Å), the formation of a new product was observed by both TLC and NMR analyses. After 3 days, an apparent 1:1 mixture of **2E**/**2Z** was produced, and treatment of this mixture with CH_2N_2 followed by flash chromatography of the crude product gave a 57% yield of a **3E**/**3Z** mixture (3:2). Acid hydrolysis of **3E** and **3Z** separately afforded the hydrochlorides of **1E** and **1Z** each in 79% yield.

The conformational information obtained from the X-ray analysis is of considerable interest (Figure 1). The C(5)–C(4)(=O(1))–NH–C(1) group is analogous to a peptide unit with dimensions close to those given by Pauling[3] et al. and the C(1)–C(11)(=O(2))–O(3)–C(12) group also resembles a planar peptide unit. Hence **4** structurally approximates a dipeptide containing a cyclopropyl amino acid. The ϕ'[(C(4)–N(1)–C(1)–C(11)] and ψ'[N(1)–C(1)–C(11)–O(3)] angles are −62.5° and −33°, respectively, and these observed values are very close to the ϕ, ψ values[4] (−49°, −26°) of a right-handed 3_{10} helix or a right-handed α-helix (−58°, −47°). Thus, amino acid modifications of this type may promote the formation of a 3_{10} or an α-helix. The ϕ_2, ψ_2, ϕ_3, ψ_3 angles for the nonhelical β-bends[5] are approximately −60°, −30°, −90°, 0° (type I) and −60°, 120°, 80°, 0° (type II), and, clearly, the ϕ' and ψ' values observed about the cyclopropyl amino acid residue also approach these values. The effect of both dehydro- and cyclopropyl amino acids on peptide conformations appear to be similar, since both of the conformational states discussed above, i.e., the 3_{10} helix and the type I β-bend, also fall within the permissible regions[6] of the (ϕ, ψ) map of dehydroalanine.

Scheme I





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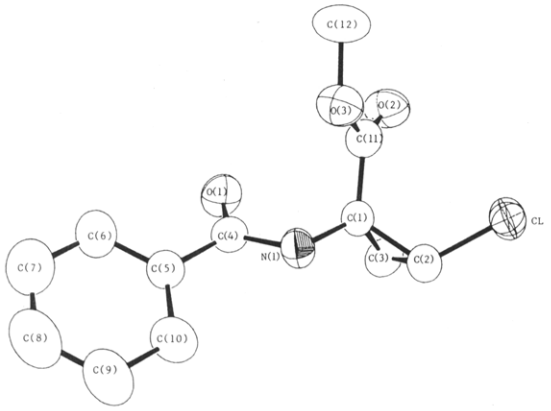

Figure 1. A thermal ellipsoid plot of the molecule.

Experimental Section

^{1}H NMR spectra were obtained on a Varian EM-390 spectrometer, and IR spectra were recorded with a Perkin-Elmer 297 infrared spectrophotometer. HPLC analyses were carried out on a Waters Associates HPLC system (M6000 pump, R401 differential refractometer). A Chromatotron (Model 7924 Harrison Research) with 4-mm-width silica plates was also used. Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected.

2-Phenyl-4-(ethoxymethylene)-5(4*H*)-oxazolone. A mixture of hippuric acid (72 g, 0.40 mol), ethyl orthoformate (60 g, 0.40 mol), and acetic anhydride (80 g, 0.78 mol) was heated at reflux for $^1/_2$ h. The reaction mixture was concentrated in vacuo to a dark red oil, which solidified on cooling to 5 °C overnight. Crystallization of crude solid twice from isopropyl alcohol gave 30 g (34%) of product: mp 94–95 °C; NMR ($CDCl_3$) δ 8.2 (m, 2 H, ortho Ar H), 7.5 (m, 3 H, meta and para Ar H), 7.35 (s, 1 H, vinyl H), 4.5 (q, 2 H, CH_2O), 1.5 (t, 3 H, CH_3); IR (KBr) 2970 (w, aliphatic), 1785 (s, C=O), 1675 (s, N=C) cm^{-1}.

2-Phenyl-4-(hydroxymethylene)-5(4*H*)-oxazolone. In a 300-mL Erlenmeyer flask were mixed 9.35 g (43 mmol) of the ethoxymethylene compound and 45 mL of concentrated HCl. After dissolving in a few seconds, the pink product rapidly precipitated, and after occasional swirling for ca. 2 h, 235 mL of ice cold water was added. The yellow precipitate was filtered, washed until neutral with cold water and then with CH_2Cl_2 (3 × 50 mL), and dried in vacuo over P_2O_5 to give 7.74 g (95%) of product: mp 139.5–141 °C (effervescent red liquid); NMR ($CDCl_3$–Me_2SO-d_6) δ 8.15 (m, 2 H, ortho Ar H), 7.9 (s, 1 H, vinyl H), 7.8 (s, 1 H, OH), 7.6 (m, 3 H, meta and para Ar H); IR (KBr) 3150–2400 (s, OH), 1780 (s, C=O), 1620–1490 (s, N=C, H bonded with OH) cm^{-1}.

2-Phenyl-4-(chloromethylene)-5(4*H*)-oxazolone (2). To a suspension of 1.20 g (6.34 mmol) of hydroxy compound in 12 mL of benzene was added 1.70 mL (19.1 mmol) of oxalyl chloride. After a vigorous evolution of gas, the mixture was stirred at room temperature 2 h and concentrated in vacuo to give 1.3 g of a light red solid, which was crystallized from THF to give 0.89 (67%) of **2** as light pink needles: mp 132–133 °C; NMR ($CDCl_3$) δ 8.2 (m, 2 H, ortho Ar H), 7.7 (m, 3 H, meta and para Ar H), 7.25 (s, 1 H, vinyl H); IR (KBr) 3075 (m, Ar H), 1800 (s, C=O), 1650 (s, N=C) cm^{-1}.

(*Z*)- and (*E*)-2-Chloro-5-phenyl-6-oxa-4-azaspiro[2.4]-hept-4-en-7-one (3). To a solution of 2.07 g (1.0 mmol) of crude **2** in 16 mL of CH_2Cl_2 was added 50 mL (1.4 mmol) of 0.3 N CH_2N_2/ether (prepared as described on Diazald bottle-method 1), evolving gas immediately. According to TLC [Et_2O/hexanes (1:5)], the reaction was finished within 7 min, producing both *Z* (R_f 0.51) and *E* (R_f 0.33) isomers. After 20 min, anhydrous $CaCl_2$ was added, and after gas evolution ceased the reaction mixture was filtered, and the solid was washed with CH_2Cl_2. The filtrate was concentrated in vacuo to give 2.16 g of an orange solid. After filtration through 4 g of silica gel (230–400 mesh) with CH_2Cl_2, a light orange solid weighing 1.94 g (89%) was obtained. Further purification and separation of isomers was obtained with use of a Chromatotron [4-mm-width plate; silica gel PF-254 with $CaSO_4 \cdot {}^1/_2H_2O$; hexane/CH_2Cl_2/EtOAc (20:10:1) eluant; 8 mL/min flow rate] to give first 0.14 g (6%) of the *Z* isomer of **3**: mp 104–105.5 °C; NMR ($CDCl_3$) δ 8.1 (m, 2 H, ortho Ar H), 7.5 (m, 3 H, meta and para Ar H), 3.9 (t, 1 H, C(2)-H), 2.3 (d, 2 H, C(3)-H). An analytical sample was obtained by purification via HPLC [30 × 0.39 cm, 10 μPorasil, CCl_4/THF (70:1), 1 mL/min].

Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32. Found: C, 59.50; H, 3.66; N, 6.30.

Secondly, the *E* isomer of **3** was obtained as a white solid weighing 1.51 g (69%): mp 140–141 °C; NMR ($CDCl_3$) δ 8.1 (m, 2 H, ortho Ar H), 7.6 (m, 3 H, meta and para Ar H), 4.05 (t, 1 H, C(2)-H), 2.45 (t, 1 H, C(3)-H), 2.15 (t, 1 H, C(3)-H); IR (KBr) 3100, 3040 (m, and Ar H), 1810 (s, C=O), 1640 (s, N=C) cm^{-1}.

Anal. Calcd for $C_{11}H_8ClNO_2$: C, 59.61; H, 3.64; N, 6.32; Cl, 16.00. Found: C, 59.50; H, 3.66; N, 6.26; Cl, 16.09.

Photoisomerization of (*E*)-2-Phenyl-4-(chloromethylene)-5(4*H*)-oxazolone (2*E*). A solution of 1.00 g (48.2 mmol) of crude **2E** in 10 mL of CH_2Cl_2 was irradiated in a 10-mm NMR tube at 3100 Å in a Rayonette reactor. After 4 h, NMR analysis showed a vinyl peak ratio, **2E** (δ 7.2)/**2Z** (δ 5.3), of 14:1; 25 h, 3:1; 65 h, 1:1. After 72 h TLC [Et_2O/hexane (1:5)] showed two spots of R_f 0.72 (**2E**) and 0.61 (**2Z**). The solution was removed from the NMR tube and concentrated in vacuo to an oil, which was dissolved in a minimum amount of CH_2Cl_2, and 24 mL (7.2 mmol) of a 0.3 N solution of CH_2N_2 in ether (prepared from Diazald) was added. After 24 h, anhydrous $CaCl_2$ was added and the solution was filtered and concentrated in vacuo to a red oil. The oil was purified by flash chromatography [230–400-mesh silica gel, 6 in. × 1 in., Et_2O/hexane (1:5) eluant, 2 mL/min flow rate]. The first 200 mL collected was concentrated in vacuo to give 0.61 g (57%) of a yellow solid: R_f [Et_2O/hexane (1:5)] 0.53 (**3Z**), 0.42 (**3E**); NMR ($CDCl_3$) δ 8.0 (m, 2 H, ortho Ar H), 7.5 (m, 3 H, meta and para Ar H), 4.0 (t, 0.6 H, **3E** C(2)-H), 3.8 (t, 0.4 H, **3Z** C(2)-H), 2.5–1.9 (m, 2 H, **3E** and **3Z** C(3)-H).

Methyl (*E*)-1-Benzamido-2-chlorocyclopropanecarboxylate (4). A solution of 0.20 g (0.90 mmol) of **3E** and 0.11 g (0.90 mmol) of DMAP in 10 mL of MeOH was stirred at room temperature for 25 min. The MeOH was removed in vacuo and the residual oil was dissolved in CH_2Cl_2, extracted with 10% citric aid (3 × 10 mL) and saturated NaCl (10 mL), dried (anhydrous $MgSO_4$), filtered, and concentrated in vacuo to give a white solid. After crystallization from CH_2Cl_2/hexane, 0.13 g (55%) of **4** as white needles was obtained: mp 167.5–168 °C; NMR ($CDCl_3$) δ 7.8 (m, 2 H, ortho Ar H), 7.4. (m, 3 H, meta and para Ar H), 3.75 (s, 3 H, CO_2CH_3), 3.57 (dd, 1 H, C(2)-H), 2.25 (t, 1 H, C(3)-H), 1.8 (t, 1 H, C(3)-H); ^{13}C NMR ($CDCl_3$) 38.77 (C(1)), 40.05 (C(2)), 24.20 (C(3)), 167.09 (C(4)), 167.52 (C(11)), 52.37 (C(12)), 132.10, 131.13, 127.65, 126.31 (C(5)–C(10), Figure 1) ppm.

Anal. Calcd for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52. Found: C, 56.56; H, 4.81; N, 5.45.

(*E*)-2-Chloro-1-aminocyclopropanecarboxylic Acid Hydrochloride (1E). A mixture of 0.50 g (2.3 mmol) of **3E**, 10 mL of concentrated HCl, 7.7 mL H_2O, and 7.7 mL of HOAc (glacial), under a N_2 atmosphere, was heated at reflux for 24 h. The reaction mixture was distilled at atmospheric pressure until 7.2 mL of distillate was collected and allowed to stand at room temperature overnight. The resulting crystalline benzoic acid was filtered, and the filtrate was extracted with ether (3 × 12 mL). The remaining benzoic acid was obtained on evaporation of the dried ether extracts in vacuo, giving a total of 0.24 g (87%). The aqueous phase was concentrated in vacuo to give a light yellow solid, which was dissolved in 1 mL of 0.2 N AcOH and purified by gel filtration through a Bio-Gel P-2 (200–400 mesh) column (2 × 90 cm, 0.2 N AcOH eluant, 10 mL/h flow rate, 5-mL fractions). Fractions 51 and 52 were combined, diluted to 60 mL with H_2O, and lyophilized to give 0.31 g (79%) of **1E**·HCl: mp 185–186 °C dec; NMR (CD_3OD) δ 4.0 (t, 1 H, C(2)-H), 2.1 (m, 2 H, C(3)-H).

Anal. Calcd for $C_4H_7Cl_2NO_2$: C, 27.93; H, 4.10; N, 8.14; Cl, 41.22. Found: C, 28.06; H, 4.14; N, 8.13; Cl, 41.32.

(*Z*)-2-Chloro-1-aminocyclopropanecarboxylic Acid Hydrochloride (1Z). The same hydrolysis conditions were repeated

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with 0.70 g (3.2 mmol) of **3Z**, 14.9 mL of concentrated HCl, 11.4 mL of H_2O, and 11.4 mL of HOAc (glacial). After distillation of 12 mL from the reaction mixture and extraction of the remainder with ether, 0.51 g of crude **1Z** was obtained. Crystallization from EtOH/ether gave 0.42 g (78%) of pure **1Z**·HCl: mp 187 °C dec; NMR (CD_3OD) δ 4.0 (m, 1 H, C(2)-H), 2.2 and 1.8 (m, 2 H, C(3)-H).

Anal. Calcd for $C_4H_7Cl_2NO_2$: C, 27.93; H, 4.10; N, 8.14; Cl, 41.22. Found: C, 28.10; H, 4.41; N, 8.12; Cl, 41.07.

Acknowledgment. We are grateful for the generous support of NIDA Grant No. DA 02938 and NSF Grant No. CHE 8122011.

Registry No. **1E**·HCl, 89363-83-7; **1Z**·HCl, 89363-84-8; **2E**, 89363-85-9; **2Z**, 89363-86-0; **3E**, 89363-87-1; **3Z**, 89363-88-2; **4**, 89363-89-3; 2-phenyl-4-(ethoxymethylene)-5(4*H*)-oxazolone, 15646-46-5; 2-phenyl-4-(hydroxymethylene)-5(4*H*)-oxazolone, 65037-88-9; hippuric acid, 495-69-2; ethyl orthoformate, 122-51-0.

Nitration of Methyl 2-Furoate with Acetyl Nitrate. On the Configurations of Six Isolated Intermediary Adducts

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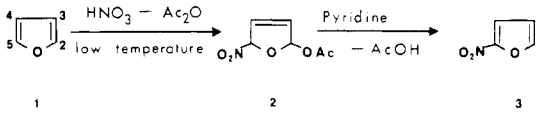
Reaction of methyl 2-furoate with acetyl nitrate afforded the isolation of six adducts whose stereochemistry was determined: (*E*)- and (*Z*)-2-carbomethoxy-2-acetoxy-5-nitro-2,5-dihydrofuran, (*E*)- and (*Z*)-2-carbomethoxy-4-acetoxy-5-nitro-4,5-dihydrofuran, and the new compounds (*E*)- and (*Z*)-2-carbomethoxy-4-nitroxy-5-nitro-4,5-dihydrofuran. The value of ^1H NMR technique in the structure determination of these compounds was demonstrated.

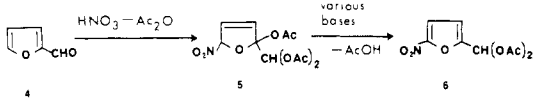
Since the beginning of this century it has been known that attempts to nitrate furan (**1**) with fuming nitric acid



1 2 3

in acetic anhydride lead to the formation of a rather stable intermediate, subsequently characterized as 2-acetoxy-5-nitro-2,5-dihydrofuran (**2**) which can be converted into 2-nitrofuran (**3**) by the action of mild base.[2,3] The isolation of this intermediate drew immediate attention since it represented at that time a contrast to the direct nitration of benzene. The structure and mode of decomposition of the intermediate were studied in considerable detail[4,5] in order to elucidate the mechanism of nitration of furan. Various structures were proposed but it was not until 1947 that structure **2**, proposed by Freure and Johnson[4] in 1931, was established.[5]

Analogous nitro acetates have since been isolated as intermediates in the nitration of several furan derivatives.[4,6-8] Under similar conditions furfural (**4**) was converted into the crystalline nitration intermediate **5**.



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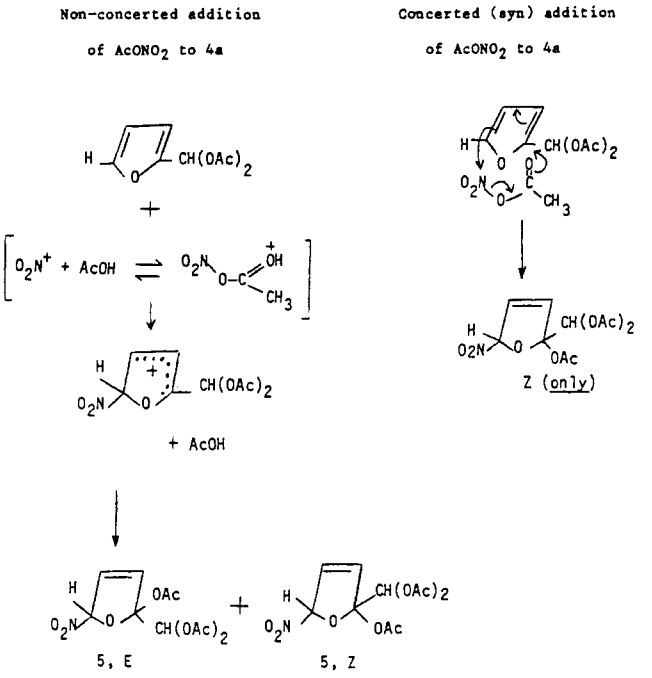
Scheme I



Crystalline **5** was assumed to be a single isomer. The stereochemical relationship between the 5 and 2 asymmetric centers was not studied until 1978 when Greene and Lewis[9] reported the characterization of **5** as a single compound by means of ^1H NMR. They suggested it to be the product of syn addition of acetyl nitrate, in line with the report of Bordwell and Garbisch that treatment of alkenes in general[10a] and, specifically, cyclopentadiene, 1-phenylcyclopentene, and 1-phenylcyclohexene,[10b] with acetyl nitrate yields the product of syn addition. However,

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