[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Rearrangement of Substituted Acyl Amino Acids to Unsaturated Azlactones

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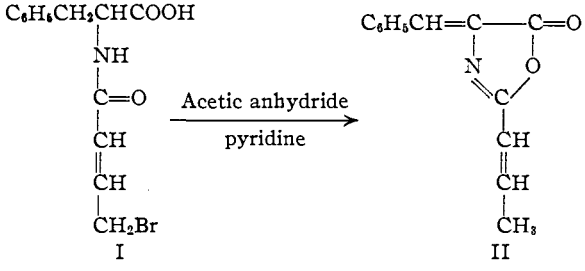
The rearrangement[2] of α-(α'-haloacyl)-amino acids to unsaturated azlactones has not been extensively studied. Two recent review articles[3,4] list eight azlactones thus prepared. It seemed of interest to investigate the scope of this unusual reaction.

Previously only α-haloacyl amino acids have been used in the reaction. The vinylog of α-haloacyl amino acid has now been prepared and found to rearrange smoothly.

N-γ-Bromocrotonyl-DL-phenylalanine (I) was prepared in 48% yield over-all from γ-bromocrotonic acid by the acylation of phenylalanine with γ-bromocrotonyl chloride in the presence of magnesium oxide. The γ-bromocrotonyl chloride was obtained by refluxing γ-bromocrotonic acid with thionyl chloride in petroleum ether.

On standing at room temperature for five minutes in a mixture of acetic anhydride and pyridine γ-bromocrotonyl-DL-phenylalanine (I) rearranged in 47% yield to 2-propenyl-4-benzylidene-5-oxazolone (II). This new azlactone did not depress the melting point of a sample prepared by the Erlenmeyer azlactone synthesis.

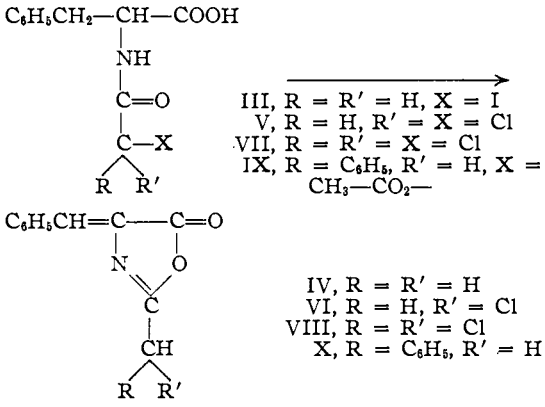


I II

In order to synthesize 2-propenyl-4-benzylidene-5-oxazolone (II) for comparison, it was necessary first to prepare N-crotonylglycine. This was accomplished by acylation of glycine with crotonyl chloride in 50% yield. Upon refluxing a mixture of N-crotonylglycine, sodium acetate, benzaldehyde, and acetic anhydride the desired 2-propenyl-4-benzylidene-5-oxazolone was obtained in 75% yield.

Bergmann and co-workers have converted N-α-chloro acyl and N-α-bromoacyl amino acids to unsaturated azlactones. It seemed likely, therefore, that N-α-iodoacylamino acids would also rearrange.

By interaction with sodium iodide for three hours in dry acetone, N-chloroacetyl-DL-phenylalanine[5] was converted to N-iodoacetyl-DL-phenylalanine (III) in 96% crude yield. The iodocompound was found to rearrange at room temperature in a mixture of acetic anhydride and pyridine to 2-methyl-4-benzylidene-5-oxazolone (IV) (50%). This azlactone did not depress the melting point of a sample[6] prepared by the Erlenmeyer synthesis.



No case of an α-dihaloacyl amino acid undergoing the rearrangement has been described. The scope of the reaction has been extended to include this type of compound. N-Dichloroacetyl-DL-phenylalanine (V) was synthesized by acylation of DL-phenylalanine with dichloroacetyl chloride. After standing for thirty minutes in a mixture of acetic anhydride and pyridine, N-dichloroacetyl-DL-phenylalanine produced a 48% yield of crude chloroacetamidocinnamic acid,[7] $ClCH_2CONHC(CHC_6H_5)COOH$, which is the hydrolysis product of the expected 2-chloromethyl-4-benzylidene-5-oxazolone (VI).

All of the compounds which have previously been reported to undergo Bergmann's rearrangement have a hydrogen on the carbon atom bearing the halogen. It seemed of interest to determine whether a compound having no α-hydrogen on the acyl group could react similarly. N-Trichloroacetyl-DL-phenylalanine (VII) has been synthesized and found to rearrange smoothly.

By acylation with trichloroacetyl chloride, N-trichloroacetyl-DL-phenylalanine (VII) was prepared in 51% yield. On standing for two hours at room temperature a mixture of the acylated amino acid, acetic anhydride, and 2,6-lutidine af-

(1) Swift Amino Acid Fellow, 1948-1949.

(2) Bergmann and Stern, *Ann.*, **44B**, 20 (1926); Bergmann, Kann and Miekeley, *ibid.*, **44B**, 135 (1926); Bergmann, Zervas and Lebrecht, *Ber.*, **64**, 2315 (1931); Doherty, Tietzmann and Bergmann, *J. Biol. Chem.*, **147**, 617 (1943); Cahill and Rudolph, *ibid.*, **145**, 201 (1942).

(3) Carter, in "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 212.

(4) Cornforth, in "The Chemistry of Penicillin," Princeton University Press, Princeton, New Jersey, 1949.

(5) Abderhalden and Herrmann, *Fermentforschung*, **10**, 153 (1929).

(6) "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 1.

(7) Bergmann, Schmitt and Miekeley, *Z. physiol. Chem.*, **187**, 264 (1930).

forded a 36% yield of 2-dichloromethyl-4-benzylidene-5-oxazolone (VIII).

The use of 2,6-lutidine as a catalyst extends the utility of the Bergmann reaction. Under the usual reaction conditions (treatment at room temperature in acetic anhydride–pyridine) no unsaturated azlactone was isolated from N-trichloroacetyl-DL-phenylalanine. The use of 2,6-lutidine, which does not form quaternary compounds readily, was successful.

It is interesting to note that N-trichloroacetyl-DL-phenylalanine, on heating at 100° in acetic anhydride for forty-five minutes, gave a 94% recovery of crude starting material. Similarly, N-dichloroacetyl-DL-phenylalanine afforded a 90% recovery of starting material after being heated at 100° for seventy minutes in acetic anhydride. However, N-chloroacetyl-DL-phenylalanine rearranges readily on heating at 100° in acetic anhydride for five minutes.

Only α-haloacylamino acids have been converted to unsaturated azlactones under the conditions of the Bergmann reaction. A compound containing an acetoxy group in the α-position was synthesized and subjected to the usual reaction conditions, and a good yield of unsaturated azlactone was produced.

N-Acetylmandelyl-DL-phenylalanine (IX) was prepared in 68% yield from acetylmandelyl chloride and phenylalanine. A 78% yield of 2-benzyl-4-benzylidene-5-oxazolone (X) was obtained on allowing IX to stand an hour at room temperature in a mixture of acetic anhydride and pyridine. The azlactone (X) did not depress the melting point of a sample[8] prepared by the Erlenmeyer procedure.

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Experimental[9]

N-γ-Bromocrotonyl-DL-phenylalanine (I).—To a suspension of 3 g. (0.0181 mole) of DL-phenylalanine, 1.1 g. (0.0546 mole) of magnesium oxide, and 50 ml. of water contained in a 100-ml. flask fitted with a stirrer and dropping funnel and cooled by an ice-bath was added over a period of an hour a solution of γ-bromocrotonyl chloride (0.0181 mole) in 20 ml. of dioxane, prepared from the corresponding acid.[10] After an additional thirty minutes of stirring, 40 ml. of ether was added and the mixture was acidified (6 *N* sulfuric acid). After extracting the acidic solution with three 40-ml. portions of ether, the combined ether extracts were dried (anhydrous sodium sulfate) and evaporated under reduced pressure. The residual sirup was crystallized from chloroform–carbon tetrachloride, affording 2.70 g. (47.5% over-all from γ-bromocrotonic acid, m. p. 126.0–126.7°) of N-γ-bromocrotonyl-DL-phenylalanine. An additional recrystallization from chloroform–carbon tetrachloride raised the melting point to 128.3–128.8°. An analytical sample was recrystallized from ethylene dichloride–ligroin and from chloroform–carbon tetrachloride, yielding colorless, diamond-shaped platelets, m. p. 128.7–129.3°.

Anal. Calcd. for $C_{13}H_{14}O_3NBr$: C, 50.01; H, 4.52; N, 4.49; Cl, 25.60. Found: C, 49.94; H, 4.59; N, 4.45; Cl, 25.93.

Rearrangement of N-γ-Bromocrotonyl-DL-phenylalanine.—After standing at room temperature for five minutes, a mixture of 0.94 g. (0.00301 mole) of γ-bromocrotonyl-DL-phenylalanine, 10 ml. of acetic anhydride, and 2 ml. of pyridine was evaporated under reduced pressure. The residue was extracted with 40 ml. of hot benzene, and the filtrate evaporatively distilled, affording 0.30 g. (46.8%, m. p. 80.0–85.0°) of crude 2-propenyl-4-benzylidene-5-oxazolone (II). An additional evaporative distillation and subsequent recrystallization from methanol–water produced yellow needles melting at 96.2–97.8°. An analytical sample was purified by recrystallization from ethanol and from ethanol–water, m. p. 98.9–99.2°.

Anal. Calcd. for $C_{13}H_{11}O_2N$: C, 73.22; H, 5.20; N, 6.57. Found: C, 73.26; H, 5.31; N, 6.60.

A sample of this material did not depress the melting point of 2-propenyl-4-benzylidene-5-oxazolone (II), prepared by the Erlenmeyer azlactone synthesis.

N-Crotonylglycine.—Crotonyl chloride[11] (38.2 g., 0.365 mole) and 435 ml. of *N* sodium hydroxide were added dropwise over a period of one hour to a cooled solution of 15 g. (0.200 mole) of glycine and 230 ml. of sodium hydroxide in a one liter round-bottomed flask equipped with a stirrer and two dropping funnels and cooled with an ice-bath. After an additional fifteen minutes stirring, the clear, colorless solution was acidified (6 *N* sulfuric acid), extracted with 500 ml. of ether (in three portions), and concentrated under reduced pressure to a volume of 300 ml., producing 10.65 g. (m. p. 161.5–163.0°) of colorless needles. The mother liquor furnished two additional crops of N-crotonylglycine (6.13 g., m. p. 160.0–161.0° and 6.06 g., m. p. 162.0–163.0°) for a total yield of 80%. On recrystallization from acetone–petroleum ether and from water an analytical sample was obtained, m. p. 163.6–163.9°.

Anal. Calcd. for $C_6H_9O_3N$: C, 50.34; H, 6.34; N, 9.79. Found: C, 50.64; H, 6.50; N, 9.68.

2-Propenyl-4-benzylidene-5-oxazolone (II).—N-Crotonylglycine (0.5 g., 0.0035 mole), 0.2 g. (0.00244 mole) of sodium acetate (anhydrous), 0.55 g. (0.005 mole) of benzaldehyde, and 6 ml. of acetic anhydride was refluxed for two hours, the solvent was then removed (reduced pressure) and the residue evaporatively distilled, giving 0.53 g. (74.6%, m. p. 73.0–84.0°) of crude product. The yellow needles were washed with dilute sodium bicarbonate solution followed with water and recrystallized from alcohol–water and from alcohol, 0.39 g., m. p. 94.6–95.5°. An additional recrystallization from ethyl acetate–petroleum ether yielded material melting at 97.0–97.5°.

N-Iodoacetyl-DL-phenylalanine (III).—A mixture of 5.7 g. (0.0236 mole) of chloroacetylphenylalanine, 4.5 g. (0.0300 mole) of sodium iodide, and 300 ml. of dry acetone was refluxed for three hours in a 500-ml. flask fitted with a stirrer, reflux condenser, and an inlet for nitrogen. The reaction mixture was filtered, the residue was washed with dry acetone, and the combined filtrate and washings were evaporated under reduced pressure. The residual sirup was taken up in absolute ether, filtered, and evaporated (reduced pressure), producing 7.5 g. (95.5%, m. p. 120.0–124.0°) of crude N-iodoacetylphenylalanine. Recrystallization from toluene afforded 5.5 g. (m. p. 139.9–140.5°) of clusters of almost colorless needles. The melting point was raised to 142–143° by a recrystallization from chloroform–carbon tetrachloride. An analytical sample was recrystallized several times from the same solvents, m. p. 145.7–146.1°.

Anal. Calcd. for $C_{11}H_{12}O_3NI$: C, 39.66; H, 3.63; N, 4.20. Found: C, 39.26; H, 3.78; N, 4.18.

Rearrangement of N-Iodoacetyl-DL-phenylalanine.—A mixture of 6 ml. of acetic anhydride and 4 ml. of pyridine was added to a solution of 1 g. (0.003 mole) of iodo-

(8) Erlenmeyer and Kunlin, *Ann.*, **307**, 163 (1899).

(9) Melting points are corrected. We are indebted to Mr. S. M. Nagy and his associates for the microanalyses.

(10) Braun, THIS JOURNAL, **52**, 3167 (1930).

(11) Staudinger, Becker and Hirzel, *Ber.*, **49**, 1991 (1916).

acetyl-DL-phenylalanine and 2 ml. of pyridine. In about ten seconds the solution had turned a dark red color. After removal of the solvent (reduced pressure), the residue was extracted with hot ligroin, affording 0.28 g. (50%, m. p. 151.3–152.7°) of 2-methyl-4-benzylidene-5-oxazolone (IV) which did not depress the melting point of an authentic sample.[6]

N-Dichloroacetyl-DL-phenylalanine (V).—To a cooled (4°) solution of 10 g. (0.0605 mole) of DL-phenylalanine and 65 ml. of *N* sodium hydroxide in a 500-ml. flask fitted with a stirrer and two dropping funnels was added dropwise over thirty-five minutes dichloroacetyl chloride (15.5 g., 0.105 mole) and 135 ml. of *N* sodium hydroxide. After stirring for an additional fifteen minutes, the reaction mixture was acidified (6 *N* sulfuric acid), producing 12.95 g. (77.4%, m. p. 132.7–135.3°) of crude dichloroacetyl-DL-phenylalanine. Recrystallization from water yielded tiny, colorless crystals (10.6 g., 137.7–138.5°). Several recrystallizations from benzene and from water yielded an analytical sample, m. p. 138.8–139.5°.

Anal. Calcd. for $C_{11}H_{11}O_3NCl$: C, 47.85; H, 4.02; N, 5.07; Cl, 25.68. Found: C, 48.12; H, 4.07; N, 5.12; Cl, 25.34.

Attempted Rearrangement of N-Dichloroacetyl-DL-phenylalanine.—A mixture of 1 g. of dichloroacetylphenylalanine and 10 ml. of acetic anhydride was heated at 100° for seventy-five minutes, then poured onto cracked ice. After evaporation under reduced pressure, 0.90 g. (90%, m. p. 126.5–131.0°) of crude starting material was recovered. Recrystallization from benzene yielded 0.72 g. (136.5–138.0°) of N-dichloroacetyl-DL-phenylalanine which did not depress the melting point of the starting material.

Rearrangement of N-Dichloroacetyl-DL-phenylalanine.—A mixture of 2 g. (0.00724 mole) of dichloroacetylphenylalanine, 20 ml. of acetic anhydride, and 2 ml. of pyridine was allowed to stand for thirty minutes at room temperature. The resulting yellow solution was evaporated under reduced pressure and the residue extracted with hot carbon tetrachloride. Upon cooling, the extract yielded in two crops 0.71 g. (m. p. 105–170°) and 0.12 g. (m. p. 175–179°) of crude material. The first crop was digested with carbon tetrachloride, leaving a residue of 0.70 g. (m. p. 177.0–178.1°). The residue was dissolved in dilute alkali and precipitated by dilute acid, giving 0.67 g. of material which melted at 182.5–183.0°. Recrystallization from water (Darco) yielded long, colorless needles (m. p. 199.5–200.3°). After several additional recrystallizations the material melted at 204.5–206.0°. (Bergmann reports[10] that N-chloroacetamidocinnamic acid melts at 207°.)

N-Trichloroacetyl-DL-phenylalanine (VII).—Over a period of eighty minutes 200 ml. of *N* sodium hydroxide and 13.5 ml. (0.121 mole) of trichloroacetyl chloride were added dropwise to a stirred solution of DL-phenylalanine (15 g., 0.0907 mole) and 95 ml. of *N* sodium hydroxide contained in a round-bottomed flask fitted with a stirrer and two dropping funnels and surrounded with an ice-bath. After an additional thirty minutes stirring, the mixture was acidified (6 *N* sulfuric acid), producing 14.5 g. (51.4%, m. p. 124.0–124.6°) of trichloroacetyl-DL-phenylalanine. Colorless needles (12.7 g., m. p. 125.5–126.6°) deposited on recrystallization from carbon tetrachloride. An analytical sample was recrystallized from ligroin and from carbon tetrachloride, m. p. 127.0–127.4°.

Anal. Calcd. for $C_{11}H_{10}O_3NCl_3$: C, 42.54; H, 3.25; N, 4.51; Cl, 34.25. Found: C, 42.62; H, 3.34; N, 4.52; Cl, 33.97.

Rearrangement of N-Trichloroacetyl-DL-phenylalanine.—A mixture of N-trichloroacetyl-DL-phenylalanine (1 g., 0.00323 mole), 10 ml. of acetic anhydride, and fifteen drops of 2,6-lutidine was evaporated under reduced pressure after standing for two hours at room temperature. The residue was extracted with ligroin, producing 0.30 g. (36.3%) of crude azlactone in two crops (0.25 g., m. p. 155.5–156.5° and 0.05 g., m. p. 140.5–150.5°). Several recrystallizations from ligroin and from alcohol–water gave an analytical sample of 2-dichloromethyl-4-benzylidene-5-oxazolone (VIII) as yellow needles, m. p. 159.1–159.6°.

Anal. Calcd. for $C_{11}H_7O_3NCl_2$: C, 51.59; H, 2.75; N, 5.47; Cl, 27.69. Found: C, 51.54; H, 2.68; N, 5.45; Cl, 27.47

Attempted Rearrangement of N-Trichloroacetyl-DL-phenylalanine.—After heating at 100° for forty-five minutes, a mixture of 1 g. of N-trichloroacetyl-DL-phenylalanine and 10 ml. of acetic anhydride was poured onto cracked ice. A 94% recovery of crude starting material was obtained in two crops (0.64 g., m. p. 95.0–110.0° and 0.30 g., m. p. 119.0–120.0°). On recrystallization from carbon tetrachloride a colorless, needle-like product (m. p. 125.5–126.5°) which did not depress the melting point of the original N-trichloroacetyl-DL-phenylalanine was obtained.

N-Acetylmandelyl-DL-phenylalanine (IX).—To a solution of 16.52 g. (0.100 mole) of phenylalanine and 110 ml. of *N* sodium hydroxide contained in a 500-ml. three-necked flask equipped with two dropping funnels and a stirrer and cooled with an ice-bath was added dropwise over a forty-minute period 25.5 g. (0.120 mole) of acetylmandelyl chloride[12] and 140 ml. of *N* sodium hydroxide. After an additional twenty minutes stirring, the mixture was acidified, giving 23.2 g. (68.1%) of a yellow oil. A solution of the oil in chloroform deposited a solid which yielded colorless needles after recrystallization from a mixture of alcohol, carbon tetrachloride, and petroleum ether, m. p. 165.0–165.2°. This compound was not obtained quite analytically pure.

Anal. Calcd. for $C_{19}H_{19}O_5N$: C, 66.85; H, 5.61. Found: C, 67.38; H, 5.64.

Rearrangement of N-(Acetylmandelyl)-DL-phenylalanine.—After standing for an hour at room temperature, a mixture of 0.5 g. (0.00147 mole) of N-(acetylmandelyl)-DL-phenylalanine, 10 ml. of acetic anhydride, and 1 ml. of pyridine was evaporatively distilled, producing a yellow liquid which soon solidified (m. p. 76.0–102.0°). Recrystallization from alcohol yielded 0.30 g. (77.7%, m. p. 106.0–106.8°) of yellow needles which did not depress the melting point of a known sample of 2-benzyl-4-benzylidene-5-oxazolone (X) prepared by the Erlenmeyer synthesis.

Summary

The rearrangement of α-(α′-haloacyl)-amino acids to unsaturated azlactones has been studied and several extensions have been developed. The following compounds were synthesized and found to rearrange smoothly: the vinylog, γ-bromocrotonyl-DL-phenylalanine; the dihaloacyl analog, N-dichloroacetyl-DL-phenylalanine; the trihaloacyl analog, N-trichloroacetyl-DL-phenylalanine; and the α-acetoxyacyl analog, N-acetylmandelyl-DL-phenylalanine.

2-Propenyl-4-benzylidene-5-oxazolone, the rearrangement product from N-γ-bromocrotonyl-DL-phenylalanine, was synthesized for comparison by the condensation of benzaldehyde and N-crotonylglycine.

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(12) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 12.