the amide. From this information it was estimated that 94% methanolysis of amides of this type (*e.g.*, V) should require 52 hr. under these conditions.

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Transformations of N-Acyl-ε-caprolactams and the Synthesis of DL-Lysine

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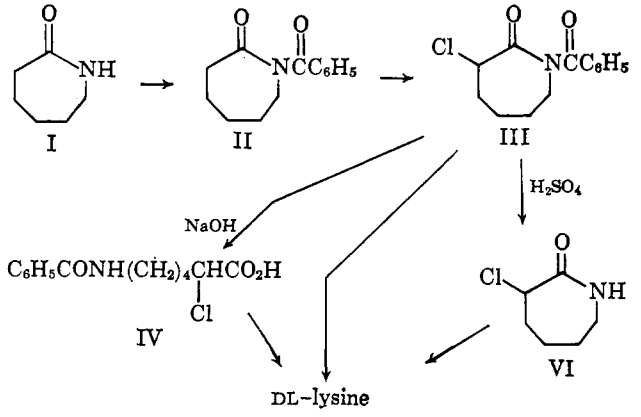
Unlike ε-caprolactam, N-benzoyl-ε-caprolactam undergoes monochlorination in the α-position to give N-benzoyl-α-chloro-ε-caprolactam. Alkaline hydrolysis of this acylated lactam furnishes ε-benzamido-α-chlorocaproic acid and cleavage of the benzoyl group with sulfuric acid provides α-chloro-ε-caprolactam. These cleavage products have been converted into DL-lysine in high over-all yield.

ε-Caprolactam has been an attractive starting material for the synthesis of lysine in recent years because of its availability and structural advantages. Introduction of the requisite amino group into ε-caprolactam by direct monochlorination in the α-position followed by ammonolysis has not been successful, the chlorination product being α,α-dichloro-ε-caprolactam.[1,2] The dichloro derivative, prepared by use of phosphorus pentachloride, has been converted into the monochloro compound and thence to lysine.[1] The monochlorocaprolactam has also been prepared from the N-chloro derivative.[3]

In contrast to the behavior of ε-caprolactam, N-benzoyl-ε-caprolactam (II) undergoes monochlorination smoothly through the agency of sulfuryl chloride to give N-benzoyl-α-chloro-ε-caprolactam (III).



The chlorination of N-benzoyl-ε-caprolactam, prepared by benzoylation in dimethylaniline, was subjected to intensive study. With chlorine only a small amount of N-benzoyl-α-chloro-ε-caprolactam could be isolated.[4] The best method consisted of chlorination with a slight excess of sulfuryl chloride in a mixture of carbon tetrachloride and cyclohexane at 40° for 24 hr. Under these conditions, N-benzoyl-α-chloro-ε-caprolactam (III) was produced in 89% yield.

Selective ring opening of N-benzoyl-α-chloro-ε-caprolactam (III) without loss of the benzoyl group or replacement of chlorine was accomplished by hydrolysis of III with sodium hydroxide in aqueous methanol. The product, ε-benzamido-α-chlorocaproic acid (IV), was found to be completely stable under the mild alkaline medium required for ring opening and was formed in 95% yield. The small amount of benzoic acid produced probably resulted from attack on the benzoyl group before ring opening. This undesired cleavage was minimized either by conducting the reaction in a solvent mixture in which III was slightly soluble or by slow addition of alkali to a hot solution of III.

The conversion of ε-benzamido-α-chlorocaproic acid into lysine was carried out by the conventional means of amination and hydrolysis.[5a,6] The over-all yield from ε-caprolactam was 73%.

Acidic hydrolysis of III provided another route to DL-lysine. In contrast to aqueous alkaline hydrolysis, concentrated sulfuric acid cleaved the benzoyl group with complete selectivity to α-chloro-ε-caprolactam (VI) in 95% yield simply by allowing a solution of III in sulfuric acid to stand at room temperature for 4 hr. The synthesis of DL-lysine was completed by ammonolysis of α-chloro-ε-caprolactam (VI) with fortified aqueous ammonia followed by hydrolysis of α-amino-ε-caprolactam (VII). These transformations have already been reported.[1a,b] Lysine was produced from VI in 72% yield or 60% from caprolactam.

Diacylamines, a class to which the N-benzoylcaprolactams belong, are known to be highly reactive toward nucleophilic and electrophilic reagents. A recent study[7] has shown in the case of N-acylbenzanilides that the stronger acid is liberated by alkaline hydrolysis and the weaker acid is liberated by cleavage in concentrated sulfuric acid. This pattern was followed upon treatment of III with these reagents.

N-Benzoyl-ε-caprolactam (II) behaved in the same manner as III toward sodium hydroxide but surprisingly underwent ring cleavage to the extent of 80% upon treatment with sulfuric acid, a reagent which effected cleavage of the benzoyl group in III.

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Experimental

Melting points are not corrected. Microanalyses were carried out by Mr. R. N. Boos and his associates.

N-Benzoyl-ε-caprolactam (II).—To a mixture of 45.2 g. (0.40 mole) of ε-caprolactam and 56.7 ml. (0.44 mole) of N,N-dimethylaniline was added 61.9 g. (0.44 mole) of benzoyl chloride. The temperature rose to 80°. The mixture was heated and stirred at 90° for 3 hr., cooled to 70°, and poured into a solution of 8 ml. of 2.5 *N* hydrochloric acid in 400 ml. of water. The crystalline lumps were broken up, collected on a filter, washed with water, and dried, 84.5 g. (97.3%), m.p. 68–70.5°, lit.[8] m.p. 67–69.5°.

N-Benzoyl-α-chloro-ε-caprolactam (III).—To a suspension of 43.4 g. (0.2 mole) of N-benzoyl-ε-caprolactam (II) in 11 ml. of carbon tetrachloride and 33 ml. of cyclohexane was added 17.0 ml. (0.21 mole) of sulfuryl chloride. The mixture was heated with stirring to 40° and maintained at 40–42° for 24 hr. The mixture was evaporated to dryness *in vacuo* and the residue was stirred with 50 ml. of isopropyl alcohol at 70° for a few minutes. The suspension was cooled to 0–5° for 1 hr. and filtered, and the product was washed with cold isopropyl alcohol and dried in air, 45.0 g. (89.3%), m.p. 120–122°, lit.[1a] m.p. 122–123°. A sample was prepared for analysis by recrystallization from ethanol, m.p. 120–121.5°.

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.61; Cl, 14.08; N, 5.57. Found: C, 61.93; H, 5.31; Cl, 14.30; N, 5.47.

ε-Benzamido-α-chlorocaproic Acid (IV) from III.—To a suspension of 10.08 g. (0.04 mole) of N-benzoyl-α-chloro-ε-caprolactam (III) in 20 ml. of methanol and 5 ml. of water was added 20.4 ml. of 1.96 *N* sodium hydroxide over 40 min. with the temperature being maintained at 2–4°. The mixture was stirred for 1 hr. at 0–3°, treated with another 2 ml. of base, and stirred for an additional 3 hr. at 0–3°. The mixture was acidified by the addition of 5.1 ml. of concentrated hydrochloric acid, diluted with 30 ml. of water, and concentrated *in vacuo* to remove the methanol. The slurry was cooled to 0–5° and filtered; the product was washed free of chloride ion, yielding 10.17 g. (94.5%), m.p. 137.5–139°, lit.[5a,b] m.p. 137.8–138.8°. No depression of melting point was observed with an authentic sample.

ε-Benzoyllysine (V) from IV.—A mixture of 13.5 g. (0.05 mole) of ε-benzamido-α-chlorocaproic acid (IV), 13 ml. of methanol, and 25 ml. of water was heated in a glass-lined shaker bomb. The mixture was cooled in a Dry Ice bath and 72 g. of liquid ammonia was added. The mixture was shaken at 105° for 1 hr., cooled, transferred to a flask, and concentrated to a thick slurry. The product was filtered and washed with water and methanol, 11.4 g. (91%), m.p. 270–272° dec., lit.[9] m.p. 268° dec.

With minor changes in procedure, the lactam (II) and the chlorolactam (III) were converted into benzoyllysine without isolation of intermediates in yields of 71 and 86%, respectively.

DL-Lysine from V.—A solution of 12.5 g. (0.05 mole) of benzoyllysine (V) in a mixture of 76.5 ml. of concentrated hydrochloric acid and 50 ml. of water was boiled under reflux for 24 hr., cooled in an ice bath, filtered to remove benzoic acid, and evaporated to dryness. The residue was triturated with 30 ml. of acetone and filtered; the cake was washed with two 15-ml. portions of acetone. The colorless DL-lysine dihydrochloride weighed 10.76 g. (98.7%). The over-all yield from caprolactam was 73.5%.

Anal. Calcd.: N, 13.39. Found: N, 13.18.

The dihydrochloride was converted into DL-lysine monohydrochloride in 95.7% yield by treatment with pyridine in ethanol.[6]

α-Chloro-ε-caprolactam (VI) from III.—To 140 ml. of concentrated sulfuric acid was added in portions 100.4 g. (0.4 mole) of N-benzoyl-α-chloro-ε-caprolactam (III), the temperature being maintained below 25°. The mixture was stirred for 1 hr. without external heating (temperature rose to 38°) and then at 50° for 2 hr. The mixture was cooled to 25°, poured onto 1 kg. of ice, neutralized with concentrated ammonium hydroxide, and extracted with three 500-ml. portions of chloroform. The chloroform solution was evaporated to give 56.2 g. (95.3%), m.p. 91.5–93°, lit. m.p. 97–98°[5b] and 92.5–93.5°.[1a] A sample, recrystallized from petroleum ether (b.p. 30–60°) melted at 92–93°.

Anal. Calcd. for $C_6H_{10}ClNO$: C, 48.80; H, 6.83; Cl, 24.03. Found: C, 48.94; H, 6.83; Cl, 23.93.

(8) H. K. Hall, Jr., M. K. Brandt, and R. M. Mason, *J. Am. Chem. Soc.*, **80**, 6420 (1958).

(9) J. von Braun, *Ber.*, **42**, 844 (1909).

The chlorolactam (VI) was reconverted to the starting benzoyllactam (III) by the procedure employed in the preparation of II, yielding 99.5%, m.p. 120–122°, no depression with II.

DL-Lysine from VI.—A mixture of 7.4 g. (0.05 mole) of α-chloro-ε-caprolactam (VI), 222 ml. of concentrated ammonium hydroxide, and 102 g. of anhydrous ammonia was heated in a bomb at 110° for 8 hr. The reaction mixture was evaporated to dryness, and the residue was triturated with a large volume of acetone. The crude α-amino-ε-caprolactam (VII) was filtered and dried, 7.9 g.

The crude aminolactam (3.0 g.) was hydrolyzed by the procedure used for V to give 3.9 g. of crude DL-lysine dihydrochloride. The dihydrochloride (1.1 g.) was converted into the monohydrochloride by treatment with pyridine in ethanol, 0.7 g., m.p. 257° dec. The yield from VI was 72%.

DL-Lysine by Ammonolysis of III.—A mixture of 8.0 g. (0.032 mole) of N-benzoyl-α-chloro-ε-caprolactam (III) and 128 ml. of concentrated ammonium hydroxide was heated in a bomb at 85–90° for 7.5 hr. The reaction mixture was evaporated to dryness. The residual oil was boiled in 200 ml. of concentrated hydrochloric acid for 13 hr. The solution was cooled to 0°, filtered to remove insoluble material, and evaporated to dryness. The solid residue was boiled with 40 ml. of alcohol for a few minutes and the mixture was cooled to 5° and filtered to remove ammonium chloride. The filtrate was treated with 3.3 ml. of pyridine, whereupon DL-lysine monohydrochloride slowly crystallized. The product was filtered and washed with alcohol, 1.2 g. (20.5%), m.p. 250° dec.

Reaction of N-Benzoyl-ε-caprolactam (II) with Sulfuric Acid.—To 35 ml. of concentrated sulfuric acid was added in portions 21.7 g. (0.1 mole) of N-benzoyl-ε-caprolactam (II), the temperature being maintained below 25°. The mixture was stirred at room temperature for 4 hr., poured onto 250 g. of ice, whereupon crystallization slowly took place. The ε-benzamidocaproic acid was filtered and triturated with water, 19.6 g. (83.5%), m.p. 79–81.5°. No depression in melting point was observed with an authentic sample.

Under similar conditions N-benzoyl-α-chloro-ε-caprolactam (III) was converted into α-chloro-ε-caprolactam (VI) in 93% yield, m.p. 91–95°.

Reaction of N-Benzoyl-ε-caprolactam (II) with Sodium Hydroxide.—To a suspension of 10.85 g. (0.05 mole) of N-benzoylcaprolactam (II) in 25 ml. of methanol and 6.2 ml. of water was added 25.2 ml. of 2 *N* NaOH over 30 min. The solution was allowed to stir at room temperature for 3 hr. and the methanol was removed by distillation at 30–35°. The residue was diluted with 10 ml. of water, acidified with a mixture of 4.5 ml. of concentrated hydrochloric acid and 4.5 ml. of water, and stirred overnight. The ε-benzamidocaproic acid was filtered and washed with water, 9.5 g. (81%), m.p. 73–77°.

Under similar conditions N-benzoyl-α-chloro-ε-caprolactam (III) was converted into ε-benzamido-α-chlorocaproic acid (IV) in 89% yield, m.p. 139–140.5°.

Mild Ammonolysis of N-Benzoyl-α-chloro-ε-caprolactam (III).—Anhydrous ammonia was passed into a boiling solution of 25.2 g. (0.10 mole) of N-benzoyl-α-chloro-ε-caprolactam in 200 ml. of methanol for 1 hr. The solution was cooled to 25°, saturated with ammonia, and allowed to stand for 3 days. The crystals were filtered, washed with methanol, and dried, 12.3 g., m.p. 159–161°. Recrystallization from water raised the melting point to 160–161°.

Anal. Calcd. for $C_{13}H_{17}ClN_2O_2$: C, 58.2; H, 6.38; Cl, 13.18; N, 10.41. Found: C, 58.15; H, 6.27; Cl, 12.9; N, 10.20.

The infrared spectrum (Nujol mull) showed peaks at 3.05–3.1 and 3.2 (N—H), and 6.0 μ, (C=O). Other bands at 6.15–6.2, 6.35–6.40, and 6.45 μ are consistent with the structure of ε-benzamido-α-chlorocaproamide (VIII).

A second crop of 3.2 g. (m.p. 155–158.5°) was obtained from the mother liquor to bring the approximate total yield to 58%.

Reaction of N-Benzoyl-ε-caprolactam (II) and Caprolactam with Ammonium Hydroxide.—A mixture of 5 g. (0.023 mole) of N-benzoyl-ε-caprolactam (II) and 92 ml. of concentrated ammonium hydroxide was heated in a bomb at 85–90° for 7.5 hr. The mixture was evaporated to dryness and triturated with 20 ml. of water, 1.84 g. (66%). The product melted at 128–130° and did not depress the melting point of benzamide.

Caprolactam was treated in a similar manner with ammonium hydroxide. A quantitative recovery of caprolactam was obtained.