[Contribution from the Chemical Research Laboratories, General Mills, Inc.]

THE SYNTHESIS OF DL-LYSINE BY OXALATE CONDENSATION[1]

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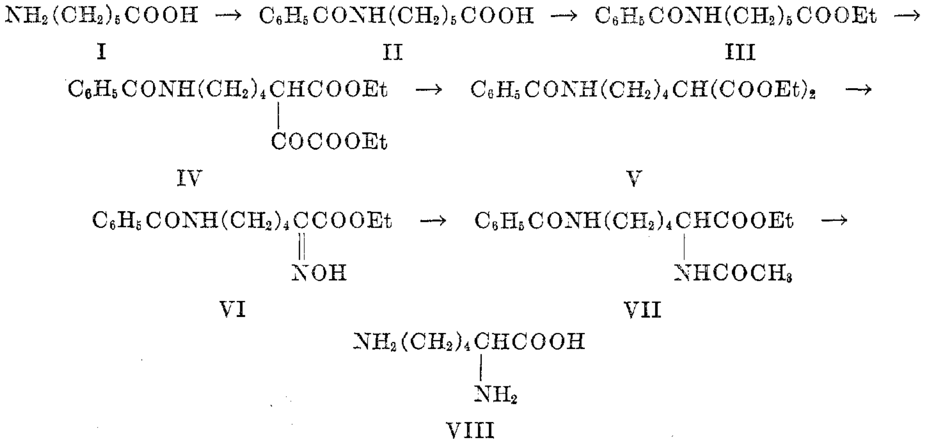
Many synthetic methods for preparing DL-lysine have been previously described (1). In one of these methods (2) ε-aminocaproic acid was used as a starting material. The present study has resulted in the development of a new method for synthesizing DL-lysine from ε-aminocaproic acid through an oxalate condensation.

The following diagram summarizes the steps used in the new synthesis:



$$\underset{\mathrm{I}}{NH_2(CH_2)_5COOH} \rightarrow \underset{\mathrm{II}}{C_6H_5CONH(CH_2)_5COOH} \rightarrow \underset{\mathrm{III}}{C_6H_5CONH(CH_2)_5COOEt} \rightarrow$$

$$\underset{\mathrm{IV}}{C_6H_5CONH(CH_2)_4\underset{\substack{|\\ COCOOEt}}{C}HCOOEt} \rightarrow \underset{\mathrm{V}}{C_6H_5CONH(CH_2)_4CH(COOEt)_2} \rightarrow$$

$$\underset{\mathrm{VI}}{C_6H_5CONH(CH_2)_4\underset{\substack{\|\\ NOH}}{C}COOEt} \rightarrow \underset{\mathrm{VII}}{C_6H_5CONH(CH_2)_4\underset{\substack{|\\ NHCOCH_3}}{C}HCOOEt} \rightarrow$$

$$\underset{\mathrm{VIII}}{NH_2(CH_2)_4\underset{\substack{|\\ NH_2}}{C}HCOOH}$$

In the present synthesis it is necessary that the amino group of ε-aminocaproic acid be blocked by an acyl group. The benzoyl group was chosen since it has no hydrogen atoms capable of replacement in the Claisen condensation used in subsequent steps. Similarly, the carboxyl group was esterified with ethanol to give III before condensation with ethyl oxalate was conducted to obtain IV.

Ainlee and King (3) and Buchman and co-workers (4) have reported condensations of esters of cinchonic acids with ε-benzamidocaproic esters in fairly low yields. Apparently, condensation of other esters with ε-benzamidocaproic esters has not been previously studied.

The yield of IV from oxalate condensation was 83% and decarbonylation to V occurred in 90% yield, making an over-all yield of 74% for the two steps. Condensation of III with ethyl carbonate, using a modification of the procedure of Wallingford, Homeyer, and Jones (5) for the preparation of alkylmalonic esters, gave a very small amount of an impure mixture containing some V. Nitrosation of V by *n*-butyl nitrite gave the α-oximino ester, VI, in 89% yield. Shivers and Hauser (6) and Barry and Hartung (7) have reported the preparations of α-oximino esters from alkylmalonic esters in yields ranging from 62–

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94%, using similar procedures. Reduction of VI to the N,N′-diacyldiamino ester, VII, was effected with zinc and acetic acid. Attempts to crystallize VII were unsuccessful, while distillation under reduced pressure led to decomposition. Therefore, VII was hydrolyzed without further purification.

Hydrolysis of VII gave a 46% yield of DL-lysine for the two steps of reduction and hydrolysis. The monohydrochloride and dihydrochloride salts and the N,N′-dibenzoyl derivative were prepared and shown by mixed melting point determinations to be identical with specimens prepared from authentic DL-lysine.

Acknowledgement. Microanalyses for C, H, and N were conducted by Mr. James Kerns of this laboratory.

EXPERIMENTAL

ε-Benzamidocaproic acid was prepared as described by Eck and Marvel (8).

Ethyl ε-benzamidocaproate. To a solution of 10 ml. of concentrated sulfuric acid in 300 ml. of absolute ethanol was added 200 g. of ε-benzamidocaproic acid. The mixture was heated under reflux for three hours and then concentrated under reduced pressure to about 350 ml. The ester was dissolved in ether and washed with water, sodium bicarbonate solution, then water, and dried over sodium sulfate. After removal of the ether, the ethyl ε-benzamidocaproate was distilled under reduced pressure. It boiled at 166–167°/0.1 mm. The yield was 201.7 g. or slightly better than 89%. The liquid ester solidified on standing at room temperature. Crystallization from ethanol gave colorless crystals melting at 37°. Ruzicka (9) prepared this compound by another method and reported the melting point 35°.

Ethyl α-ethoxalyl-ε-benzamidocaproate. Sodium ethoxide (0.5 mole) solution was prepared from 11.5 g. of sodium and 200 ml. of absolute ethanol, with the usual precautions to exclude moisture. To it were added 0.5 mole (73 g.) of ethyl oxalate and 0.5 mole (131.5 g.) of ethyl ε-benzamidocaproate. The yellow solution was warmed at 50–60° while a vacuum of 100 ± 5 mm. was applied in order to cause solvent alcohol and by-product alcohol to distill out. After about two hours no more distillate was obtained, and the viscous reaction product was worked up in the following manner. It was dissolved in 250 ml. of water and the solution was acidified to litmus with 6 *N* sulfuric acid. The liquid that separated was isolated by ether extraction, washed, and dried. It weighed 151 g., a yield of 83% of impure material.

A 2,4-dinitrophenylhydrazone was prepared in aqueous ethanol solution and crystallized from 70% ethanol. It melted at 112–113°.

Anal. Calc'd for $C_{25}H_{28}N_5O_9$: N, 12.87. Found: N, 12.63.

Ethyl α-ethoxalyl-ε-benzamidocaproate was also prepared by another procedure, under non-forcing conditions. A dry residue of 0.1 mole of sodium ethoxide was prepared from 2.3 g. of metallic sodium. To it was added 0.11 mole (16.1 g.) of ethyl oxalate and a solution of 0.1 mole (26.3 g.) of ethyl ε-benzamidocaproate in 50 ml. of dry ether. The resulting yellow solution was allowed to stand at room temperature in a stoppered flask for two days. The ether solution was extracted with 150 ml. of cold water and the aqueous extract was acidified to litmus with 6 *N* sulfuric acid. The oil that separated was isolated by ether extraction. It weighed 19.9 g. and gave the same 2,4-dinitrophenylhydrazone as the material prepared by the alternate method. The yield was 55%, somewhat inferior to that obtained under forcing conditions.

Ethyl δ-benzamidobutylmalonate. One hundred-seventeen and six-tenths grams of ethyl α-ethoxalyl-ε-benzamidocaproate, prepared according to the first method just described, was decarbonylated by heating at 155–160° under reduced pressure. The evolution of carbon monoxide ceased after about one and one-half hours. The residual liquid boiled at 189–

192°/0.2 mm. (alembic still). The colorless distillate weighed 98.1 g., a yield of about 90%. A residue of undistilled, tarry material, weighing 6.8 g., left in the distilling flask, was discarded.

A diamide derivative was prepared by saturating a solution of one gram of the malonate product in 5 ml. of ethanol with ammonia gas at 50–60° for one-half hour, and cooling the mixture in an ice-bath and saturating it with ammonia once more. The solution was diluted with 5 ml. of water, whereupon an oil separated and soon solidified; 0.6 g. m.p. 215–217°. Recrystallization from ethanol gave colorless crystals of the diamide, m.p. 217–218°.

Anal. Calc'd for $C_{14}H_{19}N_3O_3$: C, 60.65; H, 6.80; N, 15.16.
Found: C, 60.52; H, 6.66; N, 15.17.

Condensation of ethyl carbonate with ethyl ε-benzamidocaproate was conducted in the following manner: To a solution of sodium ethoxide (0.05 mole) in ethanol (20 ml.) was added 0.5 mole (59 g.) of ethyl carbonate and 0.05 mole (13.1 g.) of ethyl ε-benzamidocaproate. Ethanol was fractionally distilled at atmospheric pressure over a period of two hours. The mixture was cooled and 4 ml. of acetic acid was added. The excess ethyl carbonate was distilled off and the residual liquid was subjected to vacuum distillation. The bulk of the ethyl ε-benzamidocaproate was recovered unchanged. There was also obtained 2.5 g. of a higher-boiling fraction (169–184°/0.1 mm.) which gave the same diamide as did the ethyl ε-benzamidobutylmalonate, prepared as described above.

Ethyl α-oximino-ε-benzamidocaproate. To a solution of 0.2 gram-atom (4.6 g.) of metallic sodium in 100 ml. of absolute ethanol was added 0.2 mole (67 g.) of ethyl ε-benzamidobutylmalonate. The solution was cooled in ice and water, and the temperature was maintained at 5–10° while 0.22 mole (23 g.) of *n*-butyl nitrite was added slowly and with stirring. The mixture was stirred for one-half hour more and then concentrated at 30–35° under reduced pressure to a thick syrup. This was dissolved in 200 ml. of cold water and the solution washed with ether. The aqueous solution was made barely acid to litmus with concentrated hydrochloric acid and the oil that separated was taken up in ether. Concentration of the ether yielded a total of 52.1 g. of crystals melting in the range of 128–132°. The yield was 89% on this basis. Recrystallization from 70% ethanol raised the melting point to 133–134°.

Anal. Calc'd for $C_{15}H_{20}N_2O_4$: C, 61.6; H, 6.85; N, 9.60.
Found: C, 61.30; H, 6.69; N, 9.33.

DL-*Lysine dihydrochloride.* Ten grams of ethyl α-oximino-ε-benzamidocaproate was dissolved in a mixture of 20 ml. of glacial acetic acid and 20 ml. of acetic anhydride. The solution was stirred vigorously, and 6.7 g. of zinc dust was added in small portions so that the heat of reaction maintained the mixture at 50–55° during the reduction. The mixture was stirred for two additional hours and then filtered. The filter cake was washed with a little acetic acid; the filtrate and washing were combined and concentrated under reduced pressure on the steam-bath to remove the acetic acid and acetic anhydride. There was left 8.1 g. of a viscous, straw-colored liquid which resisted all attempts at crystallization.

Therefore, 7.0 g. of reduction product was heated under reflux with a solution of 60 ml. of concentrated hydrochloric acid and 40 ml. of water for eight hours. The benzoic acid that separated was removed and the filtrate was concentrated to a syrup under reduced pressure. DL-Lysine dihydrochloride was isolated from the syrup by precipitation with ether. The yield was 2.5 g. or about 46% on the two steps of reduction and hydrolysis. Recrystallization from ether-alcohol gave a product melting at 180–183°. Mixed melting point determinations with authentic DL-lysine dihydrochloride showed no depression.

The monohydrochloride was prepared by treatment of a solution of the dihydrochloride with pyridine to reduce the *p*H to between 5 and 6. It was recrystallized from ether-alcohol, m.p. 250–253° (dec.) and did not depress the melting point of an authentic sample of the monohydrochloride.

DL-*N,N'-dibenzoyllysine.* A solution of 0.4 g. of the DL-lysine monohydrochloride in 10 ml. of 10% sodium hydroxide was shaken vigorously with 2 g. of benzoyl chloride. Additional alkali was added from time to time to keep the mixture alkaline. The reaction mixture was acidified to litmus with hydrochloric acid and the solid that formed was dried and extracted with hot petroleum ether to remove benzoic acid. The product was crystallized from 50% ethanol as colorless leaflets melting at 144–145°. The yield was 0.3 g. A mixed melting point determination with authentic DL-N,N′-dibenzoyllysine was not depressed.

Anal. Calc'd for $C_{20}H_{22}N_2O_4$: C, 67.1; H, 6.2; N, 7.9.
Found: C, 67.7; H, 6.32; N, 8.04.

SUMMARY

A new synthesis of DL-lysine from ε-aminocaproic acid has been developed. Seven separate steps are required in the synthesis. Of these, the critical step involves condensation of an oxalate ester with an ester of acylated ε-aminocaproic acid. The yield of DL-lysine by the new route is nearly 24%.

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