ethanol, the volume was reduced to one-third by boiling, and the solution then was cooled, m.p. 204.5–206.0° (with effervescence to a clear red melt), $[\alpha]^{23}D$ +16.2 ± 0.2° (*c* 1.01 in 1 *N* HCl–ethanol (1:1)).

Anal. Calcd. for $C_{17}H_{19}O_5N$ (317.3): C, 64.3; H, 6.03; N, 4.42. Found: C, 63.7; H, 6.15; N, 4.34.

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[CONTRIBUTION FROM THE ORGANIC DIVISION, MONSANTO CHEMICAL CO.]

α-Halogenation Products of ε-Caprolactam and their Transformation to DL-Lysine[1]

BY ROBERT J. WINEMAN, EU-PHANG T. HSU AND CONSTANTINE E. ANAGNOSTOPOULOS

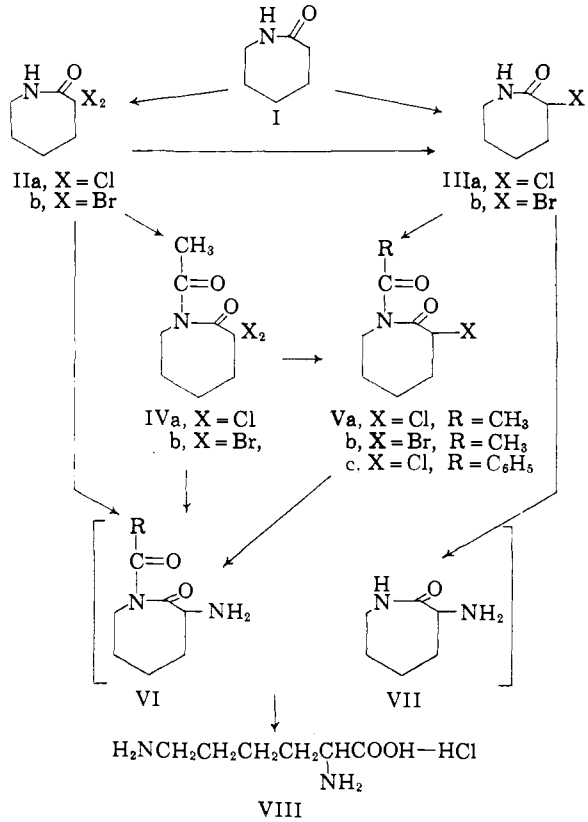
RECEIVED APRIL 11, 1958

Improved methods have been developed for the preparation of 3,3-dihalo-2-oxohexamethyleneimines. Conversions of the dihaloimines to the corresponding 3-halo-2-oxohexamethyleneimines, and transformations of the 3-halo- and 3,3-dihalo-2-oxohexamethyleneimines to DL-lysine by amination or reductive amination and acid hydrolysis are given. The latter reactions were carried out on the corresponding 1-acyl-3-halo- or 1-acyl-3,3-dihalo-2-oxohexamethyleneimines for comparison. Similarly, the transformation of 6-acetamido-2-halo- or 6-acetamido-2,2-dihalohexanoic acids to DL-lysine was made.

For the synthesis of DL-lysine, ε-caprolactam (2-oxohexamethyleneimine) frequently has been chosen as the starting material. In the last decade the increased availability of ε-caprolactam, containing all the carbon atoms and one of the nitrogen atoms required for DL-lysine in their correct state of oxidation, has gained in attractiveness as a starting material for synthetic DL-lysine. Until recently, the lactam ring has been hydrolytically cleaved, prior to halogenations and amination.[2-8] As in the classic synthesis of Eck and Marvel, an additional blocking group is introduced for protection of the ε-amino group.

It seemed apparent that the lactam might provide sufficiently stable acyl blocking of the ε-amino group to prevent its degradation in the halogenation step and to prevent effectively its interaction with an α-halogen. This study deals with the halogenation and subsequent transformations of the halocaprolactams into DL-lysine. After this work was completed, Rickenbacher and Brenner[9] reported using 3-chloro-2-oxohexamethyleneimine as an intermediate for lysine synthesis, introducing the α-amino group by interaction with sodium azide and reduction.

The initial purpose of the present investigation was to study the conversion of ε-caprolactam (I) into 3-chloro-2-oxohexamethyleneimine (IIIa), its amination to 3-amino-2-oxohexamethyleneimine (VII), and the hydrolysis of the latter to DL-lysine (VIII). Since the 3-chloro-2-oxohexamethyleneimine could not be obtained by direct halogenation of ε-caprolactam, use was made of the selective reduction of the 3,3-dichloro-2-oxohexamethyleneimine (IIa). By improved conditions for the halogenation of ε-caprolactam and selective reduction, 3-chloro-2-oxohexamethyleneimine was prepared in yields of over 80% from ε-caprolactam. The best yield of DL-lysine obtained by amination and hydrolysis of 3-chloro-2-oxohexamethyleneimine (IIIa) was 30–33% giving an over-all yield of DL-lysine of 25% from ε-caprolactam. Modifications of this route described below gave yields of 50% over-all.



The chlorination of 2-oxohexamethyleneimine was first reported by von Braun and Heymons.[10] These workers used an excess of phosphorus pentachloride, xylene as solvent and reaction at elevated temperatures. Their procedure involved a high

(1) Presented in part before the Organic Division of the American Chemical Society at the 133rd National Meeting, San Francisco, Calif., April 18, 1958.

(2) J. C. Eck and C. S. Marvel, *J. Biol. Chem.*, **106**, 387 (1934); J. C. Eck and C. S. Marvel, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 74, 76 and 374.

(3) K. Odo and S. Himizu, *J. Soc. Org. Synthet. Chem. Japan*, **11**, 386 (1953); *C. A.*, **48**, 1958 (1954).

(4) D. C. Sayles and E. F. Degering, THIS JOURNAL, **71**, 3161 (1949).

(5) A. Galat, U. S. Patent 2,519,038.

(6) A. Galat, THIS JOURNAL, **69**, 86 (1947).

(7) E. E. Howe and E. W. Pietrusza, *ibid.*, **71**, 2581 (1949).

(8) G. Steinbrunn, German Patent 855,260.

(9) H. R. Rickenbacher and M. Brenner, *Angew. Chem.*, **69**, 688 (1957); M. Brenner and H. R. Rickenbacher, *Helv. Chim. Acta*, **41**, 181 (1958).

(10) J. v. Braun and A. Heymons, *Ber.*, **63**, 502 (1930).

vacuum distillation step and the yields of 3,3-dichloro-2-oxohexamethyleneimine were less than 40%.

It was found that 3,3-dichloro-2-oxohexamethyleneimine can be prepared in 90 to 93% yields by using a combination of phosphorus pentachloride and chlorine, chloroform as the solvent and much lower reaction temperatures. In addition, this procedure did not require the distillation of any intermediate. Furthermore, the same dichloro product can be obtained in lower yields when 2-oxohexamethyleneimine is chlorinated with a combination of phosgene and chlorine, or phosphorus pentachloride and sulfuryl chloride.

Using a similar procedure and employing phosphorus pentachloride and two equivalents of bromine, 3,3-dibromo-2-oxohexamethyleneimine was obtained in 83% yield. When only one equivalent of bromine was used the 3-bromo-2-oxohexamethyleneimine was formed in 37% yield.

Attempts to synthesize the 3-chloro-2-oxohexamethyleneimine by direct chlorination of 2-oxohexamethyleneimine failed. However, 3,3-dichloro-2-oxohexamethyleneimine was easily converted in almost quantitative yields to the monochloro compound by low pressure reduction. 3,3-Dibromo-2-oxohexamethyleneimine was similarly converted in high yield to 3-bromo-2-oxohexamethyleneimine.

Amination of 3-chloro-2-oxohexamethyleneimine with excess anhydrous ammonia at 120° for one hour resulted in 85–95% conversion of the halogen to the ionic condition. Hydrochloric acid hydrolysis of the amination products resulted in 25-33% yield of DL-lysine from the lactam. Aminations at lower temperatures and longer times gave yields of the same order of magnitude. For example, excess ammonia at 70° for 12 hours resulted in only 46% reaction of 3-chloro-2-oxohexamethyleneimine, and 45% yield of crude DL-lysine, based on the 3-chloro-2-oxohexamethyleneimine consumed.

3-Bromo-2-oxohexamethyleneimine at 70° for 5 hours in the presence of excess ammonia underwent complete reaction of the halogen. Hydrolysis of this amination mixture resulted in 44% yield of DL-lysine.

Application of reductive amination conditions to 3,3-dichloro-2-oxohexamethyleneimine followed by hydrolysis resulted in a low yield (8.5% of DL-lysine.)

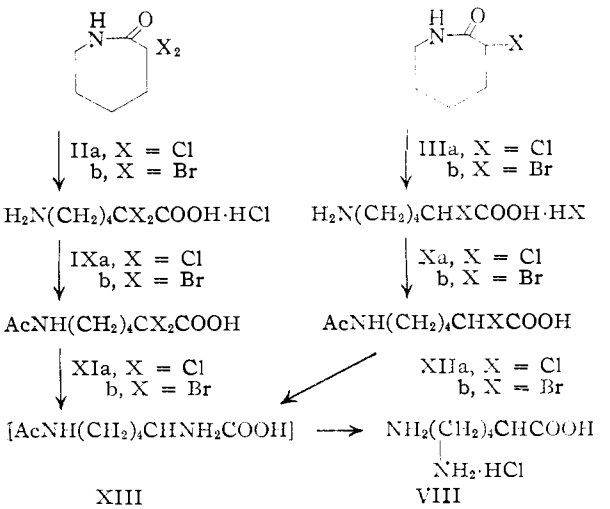
In view of the relatively low yields of DL-lysine from the amination of 3-halo or 3,3-dihalo-2-oxohexamethyleneimine, it was of interest to prepare some 1-acyl-3-halo or 1-acyl-3,3-dihalo-2-oxohexamethyleneimines to study their aminations. Since acylation of the amide nitrogen would increase the electrophilic character of the lactam carbonyl group, it was expected that this would cause the 3-halogen to have a higher reactivity in the amination.

Therefore, a series of 1-acyl compounds was prepared. The 1-acetyl-3,3-dihalo-2-oxohexamethyleneimines (IVa, IVb), were prepared readily from the corresponding halolactams in 82–86% yields by the action of excess acetic anhydride. Similarly, the 1-acetyl-3-halo-2-oxohexamethyleneimines (Va, Vb), were prepared from the corresponding monohalolactams in high yield. These compounds were also available by selective hydrogenolysis of one halogen from the 1-acetyl-3,3-dihalo-2-oxohexamethyleneimines. For example, 1-acetyl-3-chloro-2-oxohexamethyleneimine (Va) was formed in over 90% yield by atmospheric pressure hydrogenation of the dihalo compound in the presence of palladium and sodium acetate.

Amination of 1-acetyl-3-chloro-2-oxohexamethyleneimine with excess anhydrous ammonia for one hour at 120° and subsequent hydrolysis with hydrochloric acid resulted in the formation of DL-lysine in 38% yield. Similarly, the amination of the corresponding 1-acetyl-3-bromo-2-oxohexamethyleneimine resulted in 43–46% yields of DL-lysine. Use of the benzoyl group instead of acetyl gave poorer results; *e.g.*, only 12% DL-lysine was formed in amination and hydrolysis of 1-benzoyl-3-chloro-2-oxohexamethyleneimine (Vc). Reductive amination conditions applied to 1-acetyl-3,3-dichloro-2-oxohexamethyleneimine (IVa), followed by acid hydrolysis resulted in the formation of 21% DL-lysine.

Factors which might cause the relatively unsatisfactory yields in the amination and hydrolysis reactions are considered to be: Reactivity of α-halogen amides in nucleophilic displacement reactions is lower than in the corresponding acids, due to the relatively less positive character of the lactam carbonyl. Steric hindrance toward displacement reactions on the α-carbon is undoubtedly greater in the cyclic lactams than in the open chain 6-acylamido-2-halo-hexanoic acids.

The conformation of the halogen in the monohalocaprolactams is not known. The possibility exists that the halogen is more stable in the equatorial position. Steric hindrance due to the ring is greater for the displacement of halogen from the equatorial position. In an open chain compound, this is not a factor. In spite of the possible adverse electrical and steric factors, high conversions of organic to ionic halogen were possible. The nature of the side reactions was not investigated in detail. Comparative transformations involving the 6-acetamido-2-halohexanoic acids were made.



Hydrohalic acid hydrolysis of the 3-halo-or 3,3-dihalo-2-oxohexamethyleneimines (II and III) resulted in the formation of the corresponding 6-amino-2-halo, or 2,2-dihalohexanoic acid hydrohalides (IX and X) in 95% yield. These were readily acetylated to the corresponding 6-acetamido-2-halo, or 6-acetamido-2,2-dihalohexanoic acids (XI and XII) in 95% yield using acetic acid, acetic anhydride and sodium acetate. Amination of the 6-acetamido-2-halohexanoic acids in excess anhydrous ammonia followed by hydrochloric acid hydrolysis resulted in higher yields of DL-lysine than from the corresponding lactam aminations and hydrolyses. This increase in yield was also noted in the case of the reductive aminations of the dihalohexanoic acids. See Table I for the yields.

TABLE I

Hexanoic acid	Amination and hydrolysis yield of DL-lysine, % From acetylated acid	From acetylated lactam	From lactam
6-Acetamido-2-chloro-	57	38	33
6-Acetamido-2-bromo-	69	45	44
6-Acetamido-2,2-dichloro-	27	21	8.5
6-Acetamido-2,2-dibromo-	25	..	..

Acknowledgments.—The authors wish to thank Professors Robert Levine and E. E. van Tamelen and Dr. Victor Mark for helpful discussions.

Experimental[11]

3,3-Dichloro-2-oxohexamethyleneimine (IIa).—ε-Caprolactam (I) (11.3 g., 0.1 mole), was dissolved in chloroform (50 ml.) and phosphorus pentachloride (22 g., 0.11 mole) added in small portions over a period of 30 minutes, while maintaining the reaction mixture at 0–6° by external cooling. The reaction mixture was then allowed to warm up to room temperature. Gaseous chlorine now was bubbled through the reaction mixture as fast as it could be absorbed. A small increase of temperature was noticed but the reaction mixture was not cooled. When no more chlorine was absorbed bubbling was stopped and the solution was stirred for an additional hour. The chloroform then was removed under reduced pressure, with temperature maintained below 40°. The residue was poured into an ice-water mixture and the solid product was collected, washed with a small volume of cold ether and dried. The crude 3,3-dichloro-2-oxohexamethyleneimine (IIa) was dried *in vacuo* and weighed 16.6 g. (91%), m.p. 124–126°. Recrystallization from boiling ethanol gave well-formed prisms of 3,3-dichloro-2-oxohexamethyleneimine (IIa), m.p. 126–127°, reported[10] m.p. 125°.

Anal. Calcd. for $C_6H_9Cl_2NO$: Cl, 38.9. Found: Cl, 38.9.

3,3-Dichloro-2-oxohexamethyleneimine also was prepared from phosgene and chlorine. A solution of ε-caprolactam (22.6 g., 0.2 mole) in 90 ml. of chloroform was treated with gaseous phosgene for 30 minutes while the temperature was maintained between 30 and 38° by external cooling. To the solution was added 2 g. (0.01 mole) of phosphorus pentachloride and chlorine gas was passed through for 20 minutes. The reaction mixture was heated to 50° and more chlorine passed through; the solution was poured into 500 ml. of ice-water. The oil soon solidified and was collected. Repeated washings with cold ether gave 10 g. (28%) of solid, m.p. 124–126°; mixed melting point with an authentic sample of 3,3-dichloro-2-oxohexamethyleneimine gave no depression.

3,3-Dibromo-2-oxohexamethyleneimine (IIb).—ε-Caprolactam (I) (11.3 g., 0.1 mole) was dissolved in chloroform (100 ml.) and phosphorus pentachloride (41.6 g., 0.2 mole) added in small portions over a period of 30 minutes. During addition, the reaction mixture was maintained between 1 and 4° by external cooling. After all of the phosphorus pentachloride was in, 0.5 g. of zinc chloride was added followed by 32 g. (0.2 mole) of bromine. During the addition of the bromine, which took 30 minutes, the reaction mixture was allowed to reach room temperature. Stirring was continued for 5 hours and then the solvent and the unreacted bromine were removed by vacuum distillation at 40° and 20 mm. The residue was poured into an ice–water mixture and the solid was dissolved in chloroform and treated with sodium bisulfite solution to remove the last traces of bromine. Evaporation of the chloroform left a solid residue which after washing with water followed by ether yielded 22.9 g. (83.8%) of 3,3-dibromo-2-oxohexamethyleneimine (IIb), m.p. 158–160°. Recrystallization from benzene yielded pure product, m.p. 162–163.5°.

Anal. Calcd. for $C_6H_9Br_2NO$: C, 26.60; H, 3.35; Br, 58.99; N, 5.17. Found: C, 26.27; H, 3.43; Br, 59.27; N, 5.11.

3-Chloro-2-oxohexamethyleneimine (IIIa).—To a solution of the 3,3-dichloro-2-oxohexamethyleneimine (IIa), (18.2 g., 0.1 mole) in glacial acetic acid (100 ml.) were added 2 g. of 5% palladium-on-charcoal and 18 g. (0.22 mole) of sodium acetate. This mixture was placed in a shaker under hydrogen (2 atm. initial pressure) until one equivalent of hydrogen was absorbed. The catalyst and sodium chloride were removed by filtration and the filtrate concentrated under reduced pressure (36 mm.) until most of the acetic acid had been removed. The residue then was neutralized with sodium bicarbonate solution and extracted with chloroform. The chloroform extract was concentrated until crystals began to separate, then *n*-hexane (tech.) was added and a white crystalline solid precipitated. The yield of 3-chloro-2-oxohexamethyleneimine (IIIa) (m.p. 92.5–93.5°) was 22.3 g. An additional 3.4 g. (m.p. 84–88°) was obtained from the mother liquor. The total yield was 25.7 g. or 88%.

Anal. Calcd. for $C_6H_{10}ClNO$: C, 48.82; H, 6.83; Cl, 24.02; N, 9.50. Found: C, 48.53; H, 6.86; Cl, 24.13; N, 9.11.

Compound IIIa also was prepared smoothly from IIa by using 5% Pd–C, 1–2 atm. of hydrogen, in excess pyridine, or excess alcoholic ammonia. Use of anhydrous ammonia and 20 atm. of hydrogen gave impure mixtures.

Attempts to prepare IIIa directly from ε-caprolactam were unsuccessful.

3-Bromo-2-oxohexamethyleneimine (IIIb). A. By Reduction of 3,3-Dibromo-2-oxohexamethyleneimine (IIb).—3,3-Dibromo-2-oxohexamethyleneimine (IIa) (6.55 g., 0.024 mole) was reduced by the same method described for the reduction of IIa to IIIa. Glacial acetic acid (60 ml.) was used as solvent, sodium acetate (2.2 g.) as scavenger for hydrogen bromide and 5% palladium-on-charcoal (1 g.) as catalyst. The reduction was run under 2 atm. of hydrogen. The reduction proceeded much faster than in the case of the corresponding chloro compound. The yield of 3-bromo-2-oxohexamethyleneimine was 4.4 g. or 94.8%, m.p. 113–115°.

Anal. Calcd. for $C_6H_{10}BrNO$: C, 37.70; H, 5.27; Br, 41.61. Found: C, 37.78; H, 5.38; Br, 41.65.

B. **By Bromination of 2-Oxohexamethyleneimine (I).**—To a solution of 11.3 g. (0.1 mole) of ε-caprolactam in 100 ml. of chloroform was added, in small portions and over a period of 40 minutes, 20.8 g. (0.1 mole) of phosphorus pentachloride while the temperature was maintained between 2 and 5° by external cooling. After the addition of 0.2 g. of iodine, 16.0 g. (0.1 mole) of bromine was added dropwise over a period of 20 minutes. The clear solution then was allowed to stir at room temperature for one hour. The solvent and excess bromine were removed under vacuum and the residue poured into ice. The resulting solid was dissolved in chloroform and the solution washed with sodium bisulfite solution. Removal of the solvent under vacuum left a semi-solid residue which upon addition of benzene yielded 7.2 g. (37.5%) of 3-bromo-2-oxohexamethyleneimine (IIIb), m.p. 112.5–113.5°. The mixed melting point with an authentic sample of m.p. 113–115° was 113–115°.

1-Acetyl-3,3-dichloro-2-oxohexamethyleneimine (IVa).—3,3-Dichloro-2-oxohexamethyleneimine (IIa) (27.2 g., 0.15 mole) was mixed with 20 ml. of acetic anhydride and heated at 110–120° for 80 minutes, after which the excess acetic anhydride and acetic acid were removed *in vacuo*. The residue

(11) All melting points are uncorrected. Microanalyses were made by Mr. Andrew Bybell of this Laboratory. Infrared spectra were run by Dr. Bernard Katlafsky and Mr. O. E. Kinast.

was vacuum distilled, the portion boiling 100.5–102° (0.5 mm.) $n^{25}D$ 1.5177, was collected, 28.1 g. (86.4%).

Anal. Calcd. for $C_8H_{11}Cl_2NO_2$: C, 42.87; H, 4.95; N, 6.25; Cl, 31.64. Found: C, 42.38; H, 5.09; N, 5.96, Cl, 31.83.

1-Acetyl-3,3-dibromo-2-oxohexamethyleneimine (IVb).—3,3-Dibromo-2-oxohexamethyleneimine (IIb) was acetylated in the same manner as in the preparation of IVa; the yield was 82.0%, b.p. 126–127° (0.5 mm.), $n^{25}D$ 1.5640.

Anal. Calcd. for $C_8H_{11}Br_2NO_2$: C, 30.69; H, 3.54; N, 4.47; Br, 51.05. Found: C, 30.76; H, 3.49; N, 4.44; Br, 51.29.

1-Acetyl-3-chloro-2-oxohexamethyleneimine (Va). A. By Acetylation of 3-Chloro-2-oxohexamethyleneimine (IIIa).—3-Chloro-2-oxohexamethyleneimine (IIIa) was acetylated in the same manner as compound IIa, giving an 89.0% yield of Va, b.p. 94.5–96° (0.5 mm.), $n^{25}D$ 1.5104.

Anal. Calcd. for $C_8H_{12}ClNO_2$: C, 50.65; H, 6.38; N, 7.40; Cl, 18.70. Found: C, 50.30; H, 6.65; N, 7.31; Cl, 18.33.

B. **By Reduction of 1-Acetyl-3,3-dichloro-2-oxohexamethyleneimine (IVa).**—A solution of 1-acetyl-3,3-dichloro-2-oxohexamethyleneimine (IVa) (2.299 g., 0.01026 mole) in 20 ml. of acetic acid containing 0.9 g. of sodium acetate and 0.3 g. of 5% palladium-on-charcoal was allowed to take up one equivalent of hydrogen (10.26 meq.). The mixture was filtered and the acetic acid was removed from the filtrate under vacuum. The residual oil was freed of trace acetic acid by solution in chloroform, shaking with sodium bicarbonate solution and evaporation of chloroform to give 1.90 g. (98%) of an oil, $n^{25}D$ 1.5112, shown to be substantially identical to Va, from method A, by comparison of infrared spectra.

1-Acetyl-3-bromo-2-oxohexamethyleneimine (Vb).—3-Bromo-2-oxohexamethyleneimine (IIIb) was acetylated as described above for the preparation of IVa, giving a 94.6% yield of Vb, b.p. 109.5–110.5° (0.8 mm.), $n^{25}D$ 1.5321.

Anal. Calcd. for $C_8H_{12}BrNO_2$: C, 41.04; H, 5.17; N, 5.99; Br, 34.14. Found: C, 41.55; H, 5.38; N, 5.93; Br, 34.43.

1-Benzoyl-3-chloro-2-oxohexamethyleneimine (Vc).—3-Chloro-2-oxohexamethyleneimine (IIIa) (1.47 g., 0.01 mole) was dissolved in 5 ml. of pyridine and 1.58 g. (0.0112 mole) of benzoyl chloride was added. The mixture was agitated for 20 minutes and allowed to stand at room temperature for 16 hours. The solid pyridine hydrochloride was filtered off and washed with ethanol. The filtrate was evaporated to dryness yielding a colorless solid which was washed with ethanol, and dried to give 1.82 g. (72.5%) of Vc, m.p. 122–123°, reported[8] m.p. 123–124°.

Anal. Calcd. for $C_{13}H_{14}ClNO_2$: C, 62.03; H, 5.60; Cl, 14.08; N, 5.56. Found: C, 62.14; H, 5.67; Cl, 14.42; N, 5.46.

DL-Lysine Monohydrochloride (VIII). A. By Amination and Hydrolysis of 1-Acetyl-3-chloro-2-oxohexamethyleneimine (Va).—1-Acetyl-3-chloro-2-oxohexamethyleneimine (Va) (9.5 g., 0.05 mole) was dissolved in excess anhydrous ammonia (32 g.) and heated in an autoclave at 95–100° for 4 hours. The residue, after evaporation of ammonia, was dissolved in water. Titration of an aliquot with silver nitrate indicated 104% of the theoretical amount of ionic chlorine. The remainder of the solution was acidified with 37% hydrochloric acid, 12 g., and refluxed one hour. The solution was evaporated to dryness under reduced pressure, and the residue treated with absolute ethanol. The insoluble ammonium chloride was removed by filtration, and washed with ethanol. The combined filtrate and wash, 100 ml., was treated with 5 ml. of pyridine to give a *p*H 4. After standing overnight the precipitated DL-lysine monohydrochloride was filtered off, washed with ethanol and dried, 3.05 g. (33%), m.p. 253–254°; mixed melting point with an authentic sample of DL-lysine monohydrochloride, m.p. 252–253°. Also identical with an authentic sample by paper chromatographic identification.

Aminations under a variety of other conditions failed to give substantial improvements in yield. For example, amination at 120° for one hour in a 20 molar excess of ammonia in the presence of potassium iodide (105%) or nickel nitrate (5.8%), followed by hydrolysis and quantitative paper chromatographic analysis[12] resulted in yields of DL-lysine of 36–38.5%.

B. **By Amination and Hydrolysis of 1-Acetyl-3-bromo-2-oxohexamethyleneimine (Vb).**—1-Acetyl-3-bromo-2-oxohexamethyleneimine (11.7 g., 0.05 mole) was dissolved in 45 g. of anhydrous ammonia and heated at 83–90° for 2.5 hours. DL-lysine monohydrochloride, 3.0 g. (32.9%) was isolated as described in A above.

Amination in a 20 molar excess of ammonia for 10 minutes at 120° or 3 minutes at 140° gave 44–46% DL-lysine by analysis of the hydrolysis mixture.

C. **By Amination and Hydrolysis of 1-Benzoyl-3-chloro-2-oxohexamethyleneimine (Vc).**—1-Benzoyl-3-chloro-2-oxohexamethyleneimine (0.2345 g., 0.932 mmole) in a 20 molar excess of anhydrous ammonia (0.47 g., 27.6 mmoles) was heated at 120° for one hour. Analysis of the hydrolysis mixture indicated a yield of DL-lysine monohydrochloride of 0.021 g. (12.6%).

D. **By Amination and Hydrolysis of 3-Chloro-2-oxohexamethyleneimine (IIIa).**—3-Chloro-2-oxohexamethyleneimine (5.9 g., 0.04 mole) was dissolved in excess anhydrous ammonia (50 g., 2.94 moles) and heated at 70° for 12 hours. Analysis for ionic halogen indicated a conversion of 46%. After evaporation of the excess ammonia, the residue was treated with water and extracted with chloroform. Evaporation of the chloroform extracts resulted in the recovery of 3.2 g. (54%) of starting chlorolactam. The aqueous solution was hydrolyzed by the addition of 10 ml. of 37% hydrochloric acid and refluxed one hour.

The isolation of DL-lysine by the method given in A (above) resulted in 1.5 g. of DL-lysine monohydrochloride (45% based on chlorolactam consumed). Purification by solution in water and reprecipitation with ethanol gave 0.6 g. (18%) of DL-lysine monohydrochloride (VIII), m.p. 253–253.5° dec.

Amination of IIIa at 120° in 20 molar excess of ammonia followed by hydrochloric acid hydrolysis resulted in a yield of 33% DL-lysine monohydrochloride (VIII) by chromatographic analysis.[12]

E. **By Amination and Hydrolysis of 3-Bromo-2-oxohexamethyleneimine (IIIb).**—3-Bromo-2-oxohexamethyleneimine (IIIb) (3.65 g., 0.019 mole) was dissolved in excess anhydrous ammonia (40 g., 2.25 moles) and heated in an autoclave at 70° for 5 hours. Excess ammonia was evaporated and the residue dissolved in 50 ml. of water. Bromide content of the solution by silver nitrate titration was 102% of the theoretical. The solution was acidified with 15 ml. of 37% hydrochloric acid and refluxed for one hour. The resulting solution was evaporated to dryness *in vacuo*. Treatment of the residue with 30 ml. of anhydrous ethanol as in A (above), removal of ammonium chloride by filtration and adjustment of the *p*H to 4 by addition of pyridine resulted in the precipitation of DL-lysine monohydrochloride, weighing 1.50 g. (44%) after drying.

F. **By Amination and Reduction of 1-Acetyl-3,3-dichloro-2-oxohexamethyleneimine (IVa).**—Eleven and two-tenths grams (0.05 mole) of 1-acetyl-3,3-dichloro-2-oxohexamethyleneimine (IVa) was dissolved in 70 g. (4.1 moles) of anhydrous ammonia and 2 g. of 5% palladium-on-charcoal was added. The mixture was agitated and heated at 120° for two hours. Hydrogen gas at 92 atm. pressure was admitted and the mixture was reduced for 20 minutes. After the excess ammonia was evaporated, the residue was dissolved in water. Analysis for chloride indicated 99.4% of the theoretical ionic halogen, and the yield of DL-lysine by chromatographic analysis was 21%.

G. **By Amination and Reduction of 3,3-Dichloro-2-oxohexamethyleneimine (IIa).**—Using the same procedure given in F, with a reaction temperature of 120° and time of 75 minutes, DL-lysine was formed in 8% yield from IIa.

H. **By Amination of 6-Acetamido-2-halohexanoic Acids (XIIa and b).**—Aminations were carried out at 120° for one hour in the presence of 20 molar excess ammonia. Hydrochloric acid hydrolyses were done as in A (above).

Acid	DL-Lysine yield, %
6-Acetamido-2-chlorohexanoic (XIIa)	57
6-Acetamido-2-bromohexanoic (XIIb)	69

I. **By Amination, Reduction and Hydrolysis of 6-Acetamido-2,2-dihalohexanoic Acids (XIa and b).**—A solution

(12) J. F. Thompson, R. M. Zacharius and F. C. Steward, *Plant Physiol.*, **26**, 375 (1951).

of 1.21 g. (0.005 mole) of 6-acetamido-2,2-dichlorohexanoic acid (XIa) in 25 g. of anhydrous ammonia containing 0.5 g. of 5% palladium-on-charcoal was agitated and heated at 120° for two hours. Hydrogen at 70 atm. was admitted and the mixture allowed to reduce for 30 minutes. After venting the excess hydrogen and ammonia the residue was dissolved in water and filtered free of catalyst. Analysis for chloride indicated a conversion of 99.4%, and analysis for DL-lysine after hydrochloric acid hydrolysis indicated a yield of 0.245 g. (27%). Under similar conditions, except that the amination time was 25 minutes, 6-acetamido-2,2-dibromohexanoic acid (XIb) gave a yield of DL-lysine of 25%.

6-Amino-2,2-dichlorohexanoic Acid Hydrochloride (IXa).—Ten grams (0.055 mole) of 3,3-dichloro-2-oxohexamethyleneimine (IIa) was refluxed for 1.5 hours with 40 ml. of water and 20 ml. of 37% hydrochloric acid. The water and excess acid were removed *in vacuo*, and the crystalline residue washed with chloroform and acetone. After drying, the 6-amino-2,2-dichlorohexanoic acid hydrochloride weighed 11.9 g. (92%), m.p. 189.5–190.5° dec., reported[10] m.p. 191°.

6-Amino-2,2-dibromohexanoic Acid Hydrochloride (IXb).—Five grams (0.0185 mole) of 3,3-dibromo-2-oxohexamethyleneimine (IIb) was refluxed for 25 hours with 10 ml. of water, 10 ml. of 37% hydrochloric acid and 10 ml. of ethanol. The solvents and excess acid were removed *in vacuo* and the residual solid washed with chloroform and acetone. After drying, the 6-amino-2,2-dibromohexanoic acid hydrochloride weighed 3.9 g. (65%), m.p. 187–188° dec.

Anal. Calcd. for $C_6H_{12}BrClNO_2$: C, 22.14; H, 3.71; Br, 49.10; Cl, 10.89. Found: C, 22.44; H, 3.86; Br, 49.00; Cl, 11.00.

6-Amino-2-chlorohexanoic Acid Hydrochloride (Xa).—Five and five-tenths grams (0.037 mole) of 3-chloro-2-oxohexamethyleneimine (IIIa) was refluxed for one hour with 15 ml. of water and 5 ml. of 37% hydrochloric acid. Removal of the excess acid and water *in vacuo* left a glass-like residue. Upon stirring and washing repeatedly with ether, crystalline solid was obtained, which was separated by filtration and dried. The 6-amino-2-chlorohexanoic acid hydrochloride (7.1 g., 95%), was recrystallized from ethanol–ethyl acetate, m.p. 83.5–85°.

Anal. Calcd. for $C_6H_{13}Cl_2NO_2$: C, 35.65; H, 6.48; N, 6.93; Cl^-, 17.55; Cl, 35.09. Found: C, 35.53; H, 6.47; N, 7.05; Cl^-, 17.26; Cl, 35.41.

6-Amino-2-bromohexanoic Acid Hydrobromide (Xb).—3-Bromo-2-oxohexamethyleneimine (IIIb) (3.82 g., 0.02 mole) was refluxed for one hour with 10 ml. of water and 5 ml. of 47% hydrobromic acid. After removing the water and excess acid *in vacuo* an oil residue was obtained which crystallized upon treatment with ether to give 5.58 g. (96%) of 6-amino-2-bromohexanoic acid hydrobromide; recrystallized from ethanol–ethyl acetate, m.p. 118–119.5°.

Anal. Calcd. for $C_6H_{13}Br_2NO_2$: Br, 27.46. Found: Br, 27.74.

6-Acetamido-2,2-dichlorohexanoic Acid (XIa).—Four and seven-tenths grams (0.02 mole) of 6-amino-2,2-dichlorohexanoic acid hydrochloride (IXa) was mixed with 30 ml. of acetic acid, 20 ml. of acetic anhydride and 2 g. of sodium acetate and stirred at 60° for one hour. Removal of the volatile reactants at 70° *in vacuo* and treatment of the residue with water gave oily droplets which crystallized upon cooling. The 6-acetamido-2,2-dichlorohexanoic acid obtained weighed 3.6 g. (74%), m.p. 86–91°.

Anal. Calcd. for $C_8H_{13}Cl_2NO_3$: C, 39.66; H, 5.41; Cl, 29.30; N, 5.80. Found: C, 39.94; H, 5.44; Cl, 29.57; N, 5.70.

In a similar acetylation carried out at low temperature the free 6-amino-2,2-dichlorohexanoic acid was isolated. 6-Amino-2,2-dichlorohexanoic acid hydrochloride (4.72 g., 0.02 mole), 15 ml. of acetic acid and 10 ml. of acetic anhydride were stirred with 2.0 g. of sodium acetate at 23–30° for 3 hours. The solid was removed by filtration and washed with ether. Removal of the solvent from the filtrate by vacuum distillation gave an oily residue (0.1 g.) which solidified on the addition of water to give crude 6-acetamido-2,2-dichlorohexanoic acid, m.p. 87–91°. Addition of water to the solids removed by filtration (above) caused only partial solution. The undissolved solid was filtered from the aqueous solution of sodium acetate and chloride. The colorless solid, melting 174–175° dec., melted at 154–160° when mixed with the starting hydrochloride and proved to be 6-amino-2,2-dichlorohexanoic acid by analysis.

Anal. Calcd. for $C_6H_{11}Cl_2NO_2$: C, 36.01; H, 5.54; N, 7.00; Cl, 35.43. Found: C, 36.05; H, 5.64; N, 6.85; Cl, 36.01.

6-Acetamido-2,2-dibromohexanoic Acid (XIb).—Five and four-tenths grams of 6-amino-2,2-dibromohexanoic acid hydrochloride (IXb, 0.0166 mole) was mixed with 25 ml. of acetic acid, 15 ml. of acetic anhydride and stirred at 60° for 35 minutes. The reaction mixture was allowed to stand 16 hours, and the product isolated as for XIa. 6-Acetamido-2,2-dibromohexanoic acid weighing 2.4 g. (43%), m.p. 105–110°, was obtained.

Anal. Calcd. for $C_8H_{13}Br_2NO_3$: C, 29.03; H, 3.96; Br, 48.29; N, 4.23. Found: C, 29.17; H, 4.03; Br, 48.29; N, 4.21.

6-Acetamido-2-chlorohexanoic Acid (XIIa).—Two and five-hundredths grams (0.01 mole) of 6-amino-2-chlorohexanoic acid hydrochloride (Xa) was dissolved in a mixture of 15 ml. of acetic acid, 10 ml. of acetic anhydride and 1 g. of sodium acetate. The mixture was stirred at 60° for one hour and the excess reactants removed *in vacuo*. Upon addition of water to the residue an oily phase separated. Extraction four times with ethyl acetate, treating the combined extracts with sodium sulfate, filtration and removal of the solvent gave an oily residue of 6-acetamido-2-chlorohexanoic acid (2.01 g., 95%) which began to crystallize after standing two days. It was recrystallized from benzene–petroleum ether mixture, m.p. 76–78°.

Anal. Calcd. for $C_8H_{14}ClNO_3$: C, 46.25; H, 6.79; Cl, 17.07; N, 6.75. Found: C, 45.67; H, 6.63; Cl, 17.57; N, 6.78.

6-Acetamido-2-bromohexanoic Acid (XIIb).—6-Amino-2-bromohexanoic acid hydrobromide (Xb) (2.9 g., 0.01 mole) was dissolved in a mixture of 15 ml. of acetic acid, 10 ml. of acetic anhydride and 1 g. of sodium acetate. The mixture was stirred at 60–62° for one hour and solvents removed *in vacuo*. Addition of 10 ml. of water to the residue yielded a small amount of oil. The aqueous solution was extracted four times with ethyl acetate, and the combined extracts dried over sodium sulfate. Removal of the sodium sulfate and evaporation of the solvent gave 6-acetamido-2-bromohexanoic acid (2.4 g., 95%) which solidified after triturating with hexane; recrystallized twice from ethyl acetate, m.p. 92–93°.

Anal. Calcd. for $C_8H_{14}BrNO_3$: C, 38.11; H, 5.60; N, 5.56; Br, 31.70. Found: C, 38.69; H, 5.63; N, 5.57; Br, 32.00.

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