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The Preparation and Ammonolysis of α-Halogen Derivatives of ε-Caprolactam. A New Synthesis of Lysine[1]

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Improved methods have been developed for the synthesis of α-chloro-ε-caprolactam (3-chloro-2-oxohexamethyleneimine) through the dichloro derivative. In contrast to the chloro compound, it was found that α-bromo-ε-caprolactam can be prepared in one step. These syntheses were also accomplished by the direct use of cyclohexanone oxime, rather than ε-caprolactam, as starting material. The ammonolysis of α-chloro-ε-caprolactam was found to result in the formation of both α-amino-ε-caprolactam and pipecolamide (2-piperidinecarboxamide). A study of the factors which influence the course of this reaction, and methods for obtaining good yields of α-amino-ε-caprolactam are described. These reactions constitute a new method for the synthesis of lysine.

Introduction

A number of methods have been reported[2-7] for the synthesis of the essential amino acid, lysine, based on ε-caprolactam[8] as the starting material. With one exception,[6] these procedures follow a general route starting with hydrolysis of the lactam to ε-aminocaproic acid. The terminal amino group is then blocked by benzoylation, and introduction of the α-amino group is accomplished through halogenation followed by ammonolysis in aqueous ammonia systems. Hydrolysis removes the blocking acyl group and lysine is isolated as the hydrochloride salt. A variation of this general scheme was suggested by Shechter and Kirk[9] who showed that one of the intermediates, ε-benzoylamino-α-chlorocaproic acid, can be prepared by hydrolysis of α-chloro-ε-caprolactam and benzoylation of the resulting amino acid.

A more recent synthetic route[6] based on ε-caprolactam proceeds through reaction of the α-chloro lactam with sodium azide, followed by catalytic reduction of the triazo derivative to α-amino-ε-caprolactam. Hydrolysis of the latter yields lysine.

It was felt that the direct formation of α-amino-ε-caprolactam by ammonolysis of the corresponding halogen derivatives might be possible, in spite of the known susceptibility of the lactam ring to cleavage by hydrolytic and basic reagents. Indeed, it was found that under selective conditions and in the proper reaction medium, the amino lactam can be isolated in good yields. This procedure results in a synthesis of lysine in which the cyclic structure of the lactam is maintained throughout the sequence of steps leading to introduction of the α-amino group. The amido linkage of the lactam thus serves effectively for blocking the ε-amino group during the reactions which produce the final intermediate.

Such a route has the obvious advantage of eliminating the usual acylation step, and offers an alternate and convenient method for the isolation of the biologically active dextrorotatory isomer of lysine. Rickenbacher and Brenner[6] recently have reported the resolution of DL-α-amino-ε-caprolactam with L-pyrrolidonecarboxylic acid, followed by conversion of the L-amino lactam to L-lysine. A resolution using dibenzoyl-*d*-tartaric acid was independently developed in these laboratories, and will be the subject of a forthcoming publication.

Results

At the time of these investigations no eminently satisfactory procedure was available for the synthesis of α-chloro-ε-caprolactam. This compound was reported[10] to be obtained in unspecified yields from the catalytic hydrogenation of α,α-dichloro-ε-caprolactam. von Braun and Heymons[11] had prepared the dichloro lactam in yields of about 40% by reaction of ε-caprolactam with phosphorus pentachloride in xylene, followed by hydrolysis of the resulting imidyl chloride. Studies of this reaction system resulted in simple modifications which permitted yields of 85%. Yields as high as 91% were obtained by using phosphorus oxychloride as the solvent medium. Reaction of ε-caprolactam with a mixture of phosphorus oxychloride, phosphorus pentachloride and sulfuryl chloride has been reported[6] recently to yield 75–80% of the dichloro derivative.

It was found that the lactam precursor, cyclohexanone oxime, could be employed directly in these reactions to effect a more practical synthesis of the dichloro compound. In the xylene solvent system α,α-dichloro-ε-caprolactam was obtained in a yield of 75%. This reaction would appear to involve an *in situ* rearrangement of the oxime in the chlorination medium. However, the formation of a certain amount of unidentified xylene-insoluble material indicates that the reaction may not proceed by a simple stepwise rearrangement to the same intermediate as that which is involved in the chlorination of the lactam. Oxime chlorinations in the phosphorus oxychloride medium were carried out using phosphorus trichloride as a co-solvent

(1) Presented in part at the Ninth Annual Kansas City Chemistry Conference (Kansas City Section, American Chemical Society), Kansas City, Mo., November 8, 1957.

(2) J. C. Eck and C. S. Marvel, "Organic Syntheses," 2nd ed., Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, pp. 74, 76, 374.

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

(4) A. Galat, *ibid.*, **69**, 86 (1947).

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

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

(7) Y. J. Dickert and E. C. Britton, U. S. Patent 2,802,870, Aug. 13, 1957.

(8) Because of the previous common usage and convenience of terminology, the lactam nomenclature, rather than 2-oxohexamethyleneimine, has been used throughout this paper in referring to ε-caprolactam and its derivatives.

(9) H. Shechter and J. C. Kirk, THIS JOURNAL, **73**, 3087 (1951).

(10) Temmler-Werke Vereinigte Chemische Fabriken Hermann Temmler, Belgian Patent 445,599, June 30, 1942.

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

to permit low initial reaction temperatures (−10 to −20°). Resulting yields were about 80%.

It was also found that aqueous media need not be employed for converting the imidyl chloride[11] to the dichloro lactam. For example, after removal of solvent and phosphorus halides from chlorination mixtures, the residue can be treated directly with anhydrous methanol to produce α,α-dichloro-ε-caprolactam. Alternatively, xylene reaction mixtures can be concentrated to remove volatile phosphorus halides, then treated with gaseous ammonia to convert the intermediate chlorination product to the dichloro lactam.

Attempts to hydrogenate α,α-dichloro-ε-caprolactam according to the reported procedure[10] using platinum catalyst failed to result in any reduction. However, by using palladium-on-carbon in ammoniacal methanol, α-chloro-ε-caprolactam was obtained in yields as high as 89%. Raney nickel recently has been used as a catalyst for this hydrogenation.[6]

All efforts to convert ε-caprolactam directly to the monochloro derivative resulted only in isolation of the dichloro compound, even when operating with an appreciable deficiency of chlorinating agent. However, the previously unreported α-bromo-ε-caprolactam was obtained readily in yields of 65–67% by reaction of ε-caprolactam with phosphorus tribromide and bromine in benzene. Under the same conditions, cyclohexanone oxime yielded 42% of the bromo derivative. α-Iodo-ε-caprolactam was prepared in 32% yield from the monobromo derivative by conventional metathesis with sodium iodide in acetone.

The principal products of the reaction of α-chloro-ε-caprolactam with liquid ammonia were found to be α-amino-ε-caprolactam and pipecolamide. Isolation as a mixture of hydrochloride salts permitted recovery of unreacted chloro lactam and convenient separation from smaller quantities of unidentified, intractable materials.

Appreciable variation in the total yields and relative proportions of these two products was observed as the conditions and reactant ratios were varied. The data of Table I indicate a relationship between product ratio and the total amount of starting material consumed, irrespective of reaction time and temperature. However, a better correlation exists between this ratio and the final concentration of ammonium chloride, as calculated from the consumed starting material and the volume of liquid ammonia. Thus, the yield of the desired amino lactam was more than doubled (65%), and the yield of pipecolamide was decreased from 69 to 11% as the final salt concentration decreased from 3.5 to 0.15 molal. Since the total yield of identifiable products was less at the lower salt concentrations, it appears that formation of the intractable by-products is favored by the same factors which suppress the formation of pipecolamide.

TABLE I

REACTION OF α-CHLORO-ε-CAPROLACTAM WITH LIQUID AMMONIA

Mole ratio, NH_3/chloro lactam	Time, hr.	Temp., °C.	Recovd. chloro lactam, %	Final concn. NH_4Cl, molal[a]	Yield of amino lactam,[b] %	Yield of pipecolamide,[b] %
17	72.0	65	0	3.50	30	69
50	24.0	85	0	1.20	43	48
130	37.0	80	6	0.40	59	34
130	37.0	70	37	.30	62	24
95	37.0	60	60	.25	60	21
95	37.0	55	64	.20	63	18
115	30.5	55	70	.15	65	11

[a] Calcd. on basis of consumed chloro lactam. [b] Based on infrared analysis of the mixture of hydrochloride salts; see Experimental section.

Aqueous systems proved to be less satisfactory for ammonolysis of the chloro lactam. For example, hydrolysis of the product resulting from reaction in excess ammonium hydroxide and ammonium carbonate with potassium iodide catalyst[5] yielded no more than trace amounts of lysine. The major hydrolysis product was found to be pipecolic acid, which was obtained in a conversion of about 55%. Ammonolysis in concentrated ammonium hydroxide, using the reactant ratios and conditions found to be most satisfactory for the liquid ammonia medium (Table I, last reaction), resulted in the isolation of α-amino-ε-caprolactam and pipecolamide in yields of 45 and 26%, respectively.

The addition of small amounts of water to reactions carried out in liquid ammonia had a relatively minor effect. For example, the last run in Table I was repeated with the addition of two moles of water (2% solution in ammonia). Again, there was 70% recovery of starting material. The yield of amino lactam was somewhat lower (59%), and the yield of pipecolamide was increased to only 15%.

The results of reactions in liquid ammonia indicate autocatalytic formation of pipecolamide, due to the increase in ammonium chloride concentration as the reaction progresses. This conclusion was supported by initial addition of one mole of ammonium chloride to the reaction system which had yielded 65% amino lactam (Table I). Under these conditions there resulted 42% recovery of starting material, 25% yield of amino lactam and 46% yield of pipecolamide.

Various basic salts and salts of ion exchange resins were evaluated for reducing the concentration of ammonium chloride in liquid ammonia solutions. Use of 1–2 equivalents of the potassium salt form of Amberlite IRC-50, a carboxylic acid-type cation exchange resin, was found to be particularly effective. When heated at 70° for 4–5 hours with 0.5 molal solutions of ammonium chloride, 85–91% of the ammonium salt was removed from solution. Under the same conditions, the barium and calcium forms of the resin exhibited the expected low exchange capacity, resulting in decreases of soluble ammonium salt of only 28 and 14%, respectively.

Other salts which might be expected to result in ammonia-insoluble neutralization products (or water) were evaluated using a 2:1 equivalent ratio of salt to ammonium chloride. The following compounds removed ammonium chloride from 0.6 molal solutions in the indicated amounts (85°, 24 hours): sodium borate, 11%; potassium succinate, 53%; potassium bicarbonate, 68%; potas-

sium carbonate, 79%; potassium oxalate, 79%; potassium arsenite, 85%; calcium oxide, 99%. Barium and calcium carbonates effected only 16 and 25% removal of ammonium chloride from 1.2 molal solutions under these conditions.

Table II shows the results of ammonolyses carried out in the presence of various salts indicated to be effective for maintaining a low concentration of ammonium ions. Although potassium bicarbonate was only moderately effective, other additives suppressed the formation of pipecolamide to a considerable extent. Thus, under conditions which gave a 43% yield of amino lactam and 48% yield of pipecolamide in the absence of additives, addition of potassium carbonate resulted in 68% yield of amino lactam with no detectable formation of pipecolamide. In the presence of the resin salt, the reaction yielded 60% of the desired product, with only a trace of pipecolamide, even when the mole ratio of ammonia to chloro lactam was as low as 20:1.

TABLE II

REACTION OF α-CHLORO-ε-CAPROLACTAM WITH LIQUID AMMONIA IN THE PRESENCE OF VARIOUS SALTS

Conditions: 85°, 24 hr.; reactant ratios (equiv.): 1.2:1:50 (salt:chloro lactam:NH_3)

Salt	None	$KHCO_3$	CaO	$KAsO_2$	K_2CO_3	IRC-50 (K^+)[a]	IRC-50 (K^+)[b]
Recovd. chloro lactam, %	0	0	66	25	34	35	18
Yield of amino lactam, %	43	44	61	66	68	73	60
Yield of pipecolamide, %	48	25	Trace	4	0	1	Trace

[a] 80°, 26.5 hr.; equiv. ratio, 1:1:83. [b] 70°, 66.5 hr.; equiv. ratio, 1:1:20.

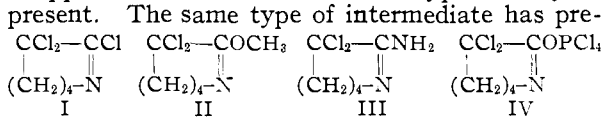
Other effects which were noted in these reaction systems were slower rates of reaction, particularly when using calcium oxide, and somewhat larger amounts of the unidentified residues.

A limited investigation of the ammonolysis of α-bromo-ε-caprolactam showed that there was very little formation of pipecolamide in the liquid ammonia medium. With only 50 moles of ammonia, amino lactam yields were as high as 61%, accompanied by about 1% of pipecolamide. Amounts of unidentified by-products were higher, and lower reaction temperatures were possible than with the chloro derivative.

Discussion

The formation of α,α-dichloro-ε-caprolactam by treatment of the imidyl chloride (I) with anhydrous methanol, rather than water, offers a convenient isolation procedure. Neutralization of hydrochloric acid is not required, and the product can be recrystallized directly from the alcoholic medium used for its formation. Since addition of anhydrous methanol to the imidyl chloride results in evolution of methyl chloride and rapid formation of the dichloro lactam rather than the expected dichloro imidyl ester (II), it appears that the ester may be cleaved readily by the hydrogen chloride formed during the methanolysis.

The use of ammonia to form the dichloro lactam in a non-aqueous medium indicates that an intermediate precursor to the imidyl chloride may actually be involved during the chlorination with phosphorus pentachloride. Thus, since phosphorus-containing neutralization products and α,α-dichloro-ε-caprolactam, rather than the expected amidine (III), are formed by passing ammonia through a concentrated xylene reaction mixture, it appears that an intermediate of type IV may be present. The same type of intermediate has previously been proposed in connection with the reactions of phosphorus pentahalides with aromatic oximes[12] and substituted benzamides.[13]



For the intended use as an intermediate in the synthesis of lysine, it is of course most desirable to obtain the monohalogenated lactam in a single step, as is possible for the bromo derivative. The lesser tendency for the monobromo intermediate to undergo further halogenation, in contrast to the chlorination process, may be due at least partly to steric factors. Molecular models of the possible intermediates, the monobromo imidyl bromide or bromophosphate ester, indicate appreciable hindrance to the approach of a second molecule of bromine.

Ammonolysis of α-chloro-ε-caprolactam in the presence of the types of additives which have been described permits the use of much lower ratios of ammonia, results in improved yields of α-amino-ε-caprolactam, and virtually eliminates pipecolamide as a by-product. The latter advantage is particularly important, since products containing appreciable amounts of the amide can be purified only with high losses. Complete separation requires hydrolysis to the corresponding mixture of neutral and basic amino acids followed by treatment with ion exchange resins according to conventional methods. This procedure is, of course, not desirable if it is the intent to isolate the biologically active L-lysine through resolution of the amino lactam intermediate.

The formation of pipecolamide from the ammonolysis of α-chloro-ε-caprolactam is not surprising in view of the fact that α-halo derivatives of ε-aminocaproic acid[14] and amides of such compounds[15] readily cyclize to form pipecolic acid or the corresponding amide. In the present case it seems likely that the formation of pipecolamide proceeds *via* an intramolecular rearrangement initiated by nucleophilic attack of ammonia at the carbonyl group. Such attack should be enhanced by the presence of the α-halogen substituent. Ammonium chloride catalysis of this reaction would appear to be analogous to the effect of ammonium salts on the ammonolysis of amides and esters.[16,17]

(12) G. H. Coleman and R. E. Pyle, THIS JOURNAL, **68**, 2007 (1946).

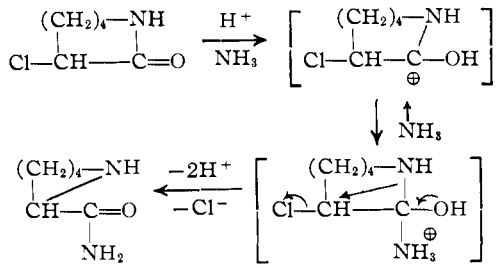
(13) N. J. Leonard and E. W. Nommensen, *ibid.*, **71**, 2808 (1949).

(14) T. Hayakawa and J. Noguchi, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **74**, 826 (1953); *C. A.*, **49**, 7566g (1955).

(15) B. T. af Ekenstam and B. G. Pettersson, *South African Patent Application* 40/57, Jan. 7, 1957.

(16) L. F. Audrieth and J. Kleinberg, "Non-Aqueous Solvents," John Wiley and Sons, Inc., New York, N. Y., 1953, pp. 88–92.

(17) L. L. Fellinger and L. F. Audrieth, THIS JOURNAL, **60**, 579 (1938).



The extent to which the rearrangement competes with the desired substitution reaction at the α-position seems to be highly dependent on the ammonium ion catalysis. This is evidenced by the practical absence of pipecolamide when suitable means are taken to reduce the concentration of soluble ammonium ions in the reaction medium.[18] A higher rate of reaction for the catalyzed rearrangement than for direct α-substitution is indicated by the lower rates of chloro lactam consumption under conditions where the latter reaction is favored.

The methods which have been investigated for reducing the concentration of ammonium ions in the reaction medium also result largely in the removal of chloride ions as insoluble metal salts at these temperatures. Evidence has been reported[19] which shows that acid catalysis in liquid ammonia may be regarded as special cases of a more general type of electrolyte catalysis, but that "onium" salts show considerably greater catalytic effect than corresponding neutral salts. Thus removal of neutral chloride salts from the ammonia solution would appear not to be essential for retarding the formation of pipecolamide.

The relatively minor effect of small amounts of water on the formation of pipecolamide in liquid ammonia is in agreement with the findings of Glasoe, Scott and Audrieth[20] concerning the lesser catalytic effect of water as compared to "onium" salts in the aminolysis of ethyl phenylacetate in *n*-butylamine. The higher proportions of pipecolamide obtained from ammonolyses in aqueous medium at comparable reactant ratios may result from a greater catalytic effect of ammonium ions, both ammonium chloride and ammonium hydroxide behaving as stronger electrolytes in this solvent.

The virtual absence of pipecolamide in products from the reaction of α-bromo-ϵ-caprolactam with ammonia indicates a more favorable relative rate of attack at the α-position for this derivative. This is in conformance with the higher degree of reactivity of alkyl bromides and the lesser degree of activation of the carbonyl function. However, the larger amounts of unidentified residues indicate that other competing reactions become important.

(18) A referee suggests that the added salts or exchange resin salts could have an effect based on the ability of these materials to remove any water which may be present due to entrainment of moisture during charging of reactants. Although the authors feel that the data and cited references support a much more pronounced effect by ammonium salts than by water, the latter is shown to have some influence, and any desiccant action of the added salts undoubtedly would be beneficial.

(19) L. F. Audrieth, L. D. Scott and O. F. Hill, THIS JOURNAL, **64**, 2498 (1942).

(20) P. K. Glasoe, L. D. Scott and L. F. Audrieth, *ibid.*, **63**, 2965 (1941).

Experimental[21]

α,α-Dichloro-ϵ-caprolactam from ϵ-Caprolactam.—To a stirred slurry of 313 g. (1.5 moles) of phosphorus pentachloride in 1 liter of xylene was added, over a period of 20 minutes, a solution of 57 g. (0.5 mole) of ϵ-caprolactam in 200 ml. of xylene. The mixture was maintained at 30–35° by external cooling during the addition, and was then heated to 80° over 20 minutes. Stirring was continued at 80–85° for 0.5 hr., and the homogeneous reaction mixture then was concentrated under reduced pressure (water aspirator) on a steam-bath. When all volatile materials had been removed, the oily residue was added, with stirring, to 500 ml. of 10% sodium carbonate. The crystalline product was filtered, washed with water, and dried to yield 77.2 g. (85%) of α,α-dichloro-ϵ-caprolactam, m.p. 118–124°. Washing with a small amount of petroleum ether raised the melting point to 124–126° (reported[11] m.p. 125°).

In one run, the reaction residue was distilled under vacuum prior to its hydrolysis. However, when the distillation was carried out on a second product, the material decomposed violently, and almost explosively, probably due to accidental overheating. As shown in the above example, distillation of the intermediate is not necessary for obtaining final product of good purity.

In a typical run using a phosphorus oxychloride medium, 68 g. (0.6 mole) of ϵ-caprolactam was added over a period of 50 minutes to a stirred slurry of 377 g. (1.8 moles) of phosphorus pentachloride in 100 ml. of the oxychloride. The temperature was maintained at 10–15° with external cooling during addition of the lactam. The mixture was then heated at reflux for 15 minutes, and the resulting solution was concentrated at atmospheric pressure until the pot temperature reached 112°. Distillation was completed under reduced pressure while heating with an oil-bath at 100°. When no further distillate could be collected at this temperature, the sirupy residue was cooled and added slowly to 400 ml. of water while stirring and cooling at 5–10°. The product was collected by filtration and washed with seven 50-ml. portions of water. The dried dichloro lactam weighed 94 g. (86%), m.p. 121–124°.

In a variation of this procedure, 34 g. (0.3 mole) of the lactam and 188 g. (0.9 mole) of phosphorus pentachloride were mixed in the dry state while cooling at 10–15°. The mixture then was heated slowly to 70° while adding 50 ml. of phosphorus oxychloride with stirring. Heating was continued at 70° for 2 hr. The reaction mixture was concentrated under reduced pressure, and the residue was hydrolyzed by addition to water. The product was washed with water and dried to yield 49.6 g. (91%) of α,α-dichloro-ϵ-caprolactam, m.p. 121–123°.

Treatment of ϵ-Caprolactam–Phosphorus Pentachloride Reaction Mixtures with Methanol and with Ammonia.—ϵ-Caprolactam (19 g., 0.17 mole) was treated with 0.5 mole of phosphorus pentachloride in xylene according to the procedure described above. The solvent and phosphorus halides were removed under reduced pressure while heating with an oil-bath to 115°. The residue was treated by the dropwise addition of 125 ml. of methanol while stirring and cooling to maintain the mixture at room temperature. The methyl chloride which was evolved during the methanol addition was collected in a trap cooled in Dry Ice–methanol. A portion of this material was transferred to a vacuum system and distilled through traps at −79 and −95° to remove methanol. A molecular weight determination gave the calculated value of 51 for methyl chloride. The methanol solution was treated with Darco, concentrated and cooled to yield 23.6 g. (77%) of α,α-dichloro-ϵ-caprolactam, m.p. 124–126°, undepressed by admixture with an authentic sample.

A solution resulting from the reaction of 28 g. (0.25 mole) of ϵ-caprolactam with 156 g. (0.75 mole) of phosphorus pentachloride in 500 ml. of xylene (*vide supra*) was concentrated under reduced pressure to less than half the initial volume. After dilution with xylene to a total volume of about 500 ml., gaseous ammonia was passed through the solution at room temperature for 0.5 hr. The precipitate was removed by filtration and washed with ether to yield 19.2 g. of a material which melted with decomposition at about 315–320°. Analysis of the crude mixture showed it to contain 11% phosphorus. The xylene filtrate was evaporated under reduced pressure to leave a dark, oily residue

(21) Melting points are uncorrected.

which crystallized on standing. No attempt was made to determine whether the residue contained additional amounts of phosphorus-containing material. This material was treated with Darco in benzene solution, and was recrystallized twice from benzene–*n*-hexane to yield 22 g. (49%) of α,α-dichloro-ε-caprolactam, m.p. 126–128°, undepressed on admixture with authentic sample.

α,α-Dichloro-ε-caprolactam from Cyclohexanone Oxime.—A solution of 57 g. (0.5 mole) of cyclohexanone oxime in 200 ml. of xylene was treated with 313 g. (1.5 moles) of phosphorus pentachloride in xylene according to the conditions and procedure described above for the reaction with ε-caprolactam. In this case, the reaction period at 80–85° was continued for a total time of 1 hr. The reaction mixture was filtered, while hot, to remove 27.4 g. of an unidentified, hygroscopic, crystalline precipitate. The filtrate was distilled under reduced pressure, and the residue was hydrolyzed in the usual manner by addition to an aqueous 10% sodium carbonate solution. There was obtained 69 g. (75%) of α,α-dichloro-ε-caprolactam, m.p. 119–123°. The product was washed with a small amount of petroleum ether to yield 66 g., m.p. 124–126°.

A slurry of 94 g. (0.45 mole) of phosphorus pentachloride in 50 ml. of phosphorus trichloride was cooled to −20° with a Dry Ice–methanol-bath. Cyclohexanone oxime (17 g., 0.15 mole) was added over a period of 30 minutes while stirring and maintaining a temperature of −10 to −20°. The mixture was allowed to warm to room temperature, and 50 ml. of phosphorus oxychloride was added. After heating at reflux for 1.5 hr., the solvent was removed under reduced pressure and the residue (42.6 g.) was added to 400 ml. of chipped ice. The hydrolysis solution was neutralized with sodium carbonate, filtered and washed with cold water to yield 22 g. (80%) of α,α-dichloro-ε-caprolactam, m.p. 116–124°. The product was recrystallized from ligroin to yield 17.5 g., m.p. 126–127°.

α-Chloro-ε-caprolactam.—A solution of 11.5 g. (0.063 mole) of α,α-dichloro-ε-caprolactam in 130 ml. of methanol saturated with ammonia was hydrogenated in a Parr apparatus in the presence of 0.12 g. of palladium-on-carbon catalyst (Baker & Co., Inc., 5% Pd–on–C). The catalyst was wet with 3 ml. of water before charging the methanol solution. The hydrogenation was carried out at 25° and an initial pressure of 47 p.s.i.g. One mole equivalent of hydrogen was absorbed in 12 minutes, the reaction being terminated at a final pressure of 36 p.s.i.g. The reaction was repeated (reduction time of 12.5 minutes), and the combined mixtures were filtered and evaporated. The crystalline residue was extracted with 500 ml. of chloroform. Evaporation of the extract, and recrystallization of the residue from ligroin, yielded 16.5 g. (89%) of α-chloro-ε-caprolactam, m.p. 92–94° (reported[9] m.p. 97–98°). A sample was recrystallized from benzene–*n*-hexane to give material melting at 93–94°.

Anal. Calcd. for $C_6H_{10}NOCl$: C, 48.8; H, 6.8; N, 9.5; Cl, 24.0. Found: C, 48.8; H, 6.8; N, 9.3; Cl, 23.9.

The product was further characterized by converting to ε-benzoylamino-α-chlorocaproic acid,[9] m.p. 135–137°, no depression on admixture with an authentic sample.[4]

The hydrogenation was carried out in the presence of 0.5 equivalent of ammonia (using a standardized solution of ammonia in methanol) with 0.24 g. of the catalyst. Only 60% of the theoretical quantity of hydrogen was absorbed in 2 hr., and the reaction was discontinued. With the same catalyst charge in the presence of one equivalent of ammonia, the theoretical quantity of hydrogen was absorbed in 9 minutes. After 70 minutes the total hydrogen uptake was only 1.2 equivalents. Two such runs were terminated after theoretical hydrogen absorption. The solutions were combined and worked up as before to yield 16.4 g. (88%) of α-chloro-ε-caprolactam, m.p. 92–93°.

α-Bromo-ε-caprolactam.—A solution of 17 g. (0.15 mole) of ε-caprolactam in 50 ml. of benzene was added to a mixture of 48 g. (0.3 mole) of bromine and 81 g. (0.3 mole) of phosphorus tribromide in 50 ml. of benzene. The addition was carried out while stirring and cooling to maintain a temperature of 10–15°. The reaction mixture was diluted with 100 ml. of benzene and heated at 45° for 5.5 hr. The lower layer was added to chipped ice. After warming to room temperature, the hydrolysis solution was filtered, and the product was washed with cold water. A small amount of additional product was obtained by chloroform extraction of the aqueous filtrate. The combined product was dried to yield 19.2 g. (67%) of crude α-bromo-ε-caprolactam, m.p. 109–113°. A sample was recrystallized from benzene–*n*-hexane to give purified product melting at 110–111°.

Anal. Calcd. for $C_6H_{10}NOBr$: C, 37.5; H, 5.2; N, 7.3; Br, 41.6. Found: C, 37.5; H, 4.9; N, 7.3; Br, 41.0.

The reaction was repeated using half the quantity (41 g.) of phosphorus tribromide with the full two moles of bromine. There was obtained 19.4 g. of crude α-bromo-ε-caprolactam, m.p. 105–109°, which was recrystallized to yield 15.5 g. (54%) of the pure product. When the reaction temperature was increased to 80° for 0.5 hr., there was evidence of decomposition. The yield of crude product, m.p. 100–105°, was only 3.8 g. (13%).

A similar reaction was carried out using phosphorus trichloride, rather than the tribromide, in a phosphorus oxychloride solvent medium. Hydrolysis of the reaction product yielded 13.5 g. of crude material, m.p. 133–135°. Repeated recrystallization from benzene–*n*-hexane raised the melting point to 151–153°, but bromine analyses remained 2–3% above the calculated value for the dibromo lactam.

A reaction of 17 g. (0.15 mole) of cyclohexanone oxime with 48 g. (0.3 mole) of bromine and 81 g. (0.3 mole) of phosphorus tribromide in benzene was carried out according to the procedure and conditions described above. The hydrolysis solution was neutralized with sodium carbonate, decolorized with sodium bisulfite, and saturated with sodium chloride. The product was collected by filtration, washed with a small amount of cold water, and dried. Recrystallization from ligroin yielded 12.2 g. (42%) of α-bromo-ε-caprolactam, m.p. 112–113°.

α-Iodo-ε-caprolactam.—A stainless-steel reactor was charged with 5.8 g. (0.03 mole) of α-bromo-ε-caprolactam, 6.7 g. (0.045 mole) of sodium iodide and 100 ml. of dry acetone. The reactor was heated at 100° for 22 hr. The mixture was filtered, and the filtrate was evaporated under reduced pressure. The residue was stirred with 200 ml. of a 10% aqueous sodium carbonate solution and allowed to stand at room temperature for 2 days. The crude product was collected by filtration, dried and recrystallized from benzene–petroleum ether to yield 2.3 g. (32%) of α-iodo-ε-caprolactam, m.p. 127–128°.

Anal. Calcd. for $C_6H_{10}NOI$: C, 30.1; H, 4.2; N, 5.9. Found: C, 30.2; H, 4.3; N, 5.9.

Infrared Analysis of Ammonolysis Product Mixtures.—Mixtures of α-amino-ε-caprolactam and pipecolamide hydrochloride were analyzed by infrared spectra (KI disk) using the relative absorbance at 12.17 μ for α-amino-ε-caprolactam hydrochloride and 11.12 μ for pipecolamide hydrochloride. Evaluation of the analytical method with standard mixtures indicated an accuracy of ±2% for amino lactam contents within the range of 20–80%. For values falling outside this range the accuracy was ±5%. Standard samples of the amino lactam were prepared from lysine by the method of Adamson,[22] and pipecolamide was prepared from α-chloro-ε-caprolactam as described below.

Reactions of α-Chloro-ε-caprolactam with Liquid Ammonia.—In a typical run, a 750-ml. stainless-steel reactor was cooled in a Dry Ice-bath and charged with 15.1 g. (0.102 mole) of α-chloro-ε-caprolactam and 275 ml. (11.7 moles) of liquid ammonia (refrigeration grade, containing less than 0.01% water). The calculated volume of ammonia was previously condensed at about −65° in a graduated flask protected from atmospheric moisture. The sealed reactor was heated on a rocking shaker at 55° for 30.5 hr. Excess ammonia was vented at room temperature, and the reactor was then pumped under vacuum to remove residual ammonia. The residue was dissolved in 125 ml. of methanol, and the solution was concentrated under reduced pressure to about one-half the initial volume. The concentrate was diluted with methanol to 100 ml. and was acidified by addition of a methanol solution of hydrogen chloride. The acidic solution was distilled to dryness under reduced pressure, and the residue was extracted with 125 ml. of acetone. The dried, acetone-insoluble product (3.7 g., m.p. 259–271°) was shown by infrared analysis to contain 87% α-amino-ε-caprolactam hydrochloride and 13% pipecolamide hydrochloride. The solvent was distilled from the acetone solution, and the residue was recrystallized from ligroin to yield 10.6 g. (70% recovery) of α-chloro-ε-caprolactam, m.p. 90–92°. The ligroin extraction

(22) D. W. Adamson, *J. Chem. Soc.*, 39 (1943).

left 0.3 g. of a dark, gummy residue. Distillation of the ligroin mother liquor yielded an additional 0.4 g. of oily residue. Based on the product analysis, yields of amino lactam and pipecolamide were 64 and 9.6%, respectively.

The above reaction was repeated by the same procedure to determine reproducibility. There was obtained 3.9 g. of product, m.p. 253–263°, which analyzed for 85% amino lactam and 15% pipecolamide as the hydrochlorides. Recovered chloro lactam was 10.6 g. (70%), m.p. 90–93°. The product corresponded to a 66% yield of α-amino-ε-caprolactam and 10.6% yield of pipecolamide.

The reaction was repeated a third time with the addition of 5.5 g. (0.103 mole) of ammonium chloride. The chloride and chloro lactam were dried to constant weight in a vacuum oven, and analyzed for less than 0.03% water. The reactor was dried, flushed with dry nitrogen, and charged by weight with liquid ammonia through direct connection with the ammonia cylinder. After completion of the reaction and removal of ammonia, the residue was treated in methanol with 70 g. of dried Amberlite IRA-400(OH^-)[23] anion exchange resin. The product was isolated from the methanol filtrate as described above. Recovered chloro lactam was 6.3 g. (41.7%), m.p. 92–94°. The product, 6.9 g., m.p. 208–222°, analyzed for 35% α-amino-ε-caprolactam and 65% pipecolamide, corresponding to yields of 25 and 46%, respectively.

Other reactions of the chloro lactam with liquid ammonia were carried out as described in the first example. Conditions of time and temperature and the reactant ratios were varied as shown in Table I. In one case water was added in the amount of 2% by weight based on ammonia. As shown in the description of the preparation of pipecolamide (*vide infra*), the scale of reaction was correspondingly increased when employing lower ratios of ammonia to lactam.

Isolation of Pipecolamide Hydrochloride.—The pressure reactor was charged, as above, with 54 g. (0.37 mole) of α-chloro-ε-caprolactam and 145 ml. (6.14 moles) of liquid ammonia. The mixture was heated, with agitation, at 65° for 72 hr. After venting excess ammonia, the residue was dissolved in 350 ml. of methanol. The solution was concentrated, rediluted to the original volume, and filtered while hot. The cooled filtrate was acidified with gaseous hydrogen chloride and allowed to stand in the refrigerator overnight. The product was collected by filtration and dried to yield 21.4 g. of pipecolamide hydrochloride, m.p. 252–254°. A sample was recrystallized from methanol and washed with ether to give material, m.p. 254–255° (reported[24] m.p. 254°).

Anal. Calcd. for $C_6H_{13}N_2OCl$: C, 43.8; H, 8.0; N, 17.0; Cl, 21.5. Found: C, 43.7; H, 7.3; N, 16.8; Cl, 21.6.

The product was further characterized by hydrolysis in hydrochloric acid. A solution of 4.8 g. (0.029 mole) of the amide hydrochloride in 110 ml. of 20% hydrochloric acid was refluxed for 6 hr. The solution was distilled to dryness under reduced pressure, and the residue was extracted with 70 ml. of hot absolute ethanol. Ether (125 ml.) was added to the cooled alcohol solution, and the precipitate was collected by filtration to yield 4.3 g. (0.026 mole, 90% yield) of pipecolic acid hydrochloride, m.p. 255–260°, undepressed on admixture with authentic sample, m.p. 258–260°, prepared by the method of Reckhow and Tarbell.[25] The infrared spectrum was in agreement with that of the authentic sample.

The methanol filtrate from the above isolation of pipecolamide was evaporated, and the residue was found to contain no acetone-soluble material. Recrystallization from methanol by addition of ether yielded 38.4 g. of a crude product mixture shown by infrared analysis to contain about 53% pipecolamide hydrochloride and 47% amino lactam hydrochloride. From the mother liquor was obtained 4.6 g. of unidentified residue. Based on the analysis of the product mixture, total yields were 69% pipecolamide and 30% α-amino-ε-caprolactam.

Reaction of α-Bromo-ε-caprolactam with Liquid Ammonia. The reactor was charged with 23 g. (0.12 mole) of α-bromo-ε-caprolactam and 142 ml. (6.0 moles) of liquid ammonia. The mixture was heated, with agitation, at 50° for 24 hr. Excess ammonia was vented, and the residue was dissolved in 300 ml. of absolute ethanol. The solution was concentrated under reduced pressure, rediluted to the original volume, and slurried with 31 g. of dried Amberlite IRA-400[23] anion exchange resin in the free base form. A precipitate which had formed in the ethanol concentrate disappeared during the resin treatment. The resin was filtered, and the filtrate was concentrated and acidified with an ethanol solution of hydrogen chloride to precipitate the product. After washing with acetone, the material was dried to yield 9.4 g. of α-amino-ε-caprolactam hydrochloride, m.p. 282–286°. The infrared spectrum was in agreement with that of an authentic sample,[22] m.p. 293–295° (reported[22] m.p. 294–296°). The filtrate was concentrated, and addition of acetone precipitated a second crop. After washing with acetone there was obtained 2.8 g., m.p. 258–266°. Infrared analysis showed this material to contain about 96% α-amino-ε-caprolactam hydrochloride, the remainder being pipecolamide hydrochloride. Total yield of amino lactam was 61.5%, and the yield of pipecolamide was less than 1%. The combined filtrates and washings were evaporated to yield 7.2 g. of sirupy residue. Extraction with ligroin failed to yield any crystalline material.

Reactions of α-Chloro-ε-caprolactam with Aqueous Ammonia.—A 200-ml., stainless-steel reactor was charged with 5 g. (0.034 mole) of the chloro lactam, 39 g. (0.4 mole) of ammonium carbonate, 68 g. (1.1 moles) of concentrated (28%) ammonium hydroxide and 0.2 g. of potassium iodide. The reactor was heated on a rocking shaker at 50° for 12 hr., and then at 60° for 3.5 hr. The mixture was discharged, with addition of water, and filtered. After boiling for 0.5 hr. to decompose the carbonate, the solution was distilled under reduced pressure at a bath temperature of 80°. The sirupy residue was hydrolyzed by refluxing 11 hr. in 100 ml. of 20% hydrochloric acid. The hydrolysis mixture was evaporated under vacuum, and the residue was extracted with 50 ml. of boiling absolute ethanol. Addition of 60 ml. of ether to the cooled ethanol solution precipitated 3.1 g. of product, m.p. 229–234°. The infrared spectrum showed this material to be primarily pipecolic acid hydrochloride (55% conversion) with what appeared to be a trace of lysine dihydrochloride. A sample of the product mixture was treated with aqueous picric acid to yield a small amount of lysine dipicrate, m.p. 184–186° (reported[22] m.p. 186–188°), undepressed by admixture with an authentic sample.

In a second run, using the 750-ml. reactor, a solution of 7.0 g. (0.047 mole) of the chloro lactam in 325 g. (5.4 moles) of concentrated (28%) ammonium hydroxide was heated at 55° for 30.5 hr. The mixture was evaporated under reduced pressure, and the dried residue (7.2 g.) was dissolved in 100 ml. of methanol and acidified with a methanol solution of hydrogen chloride. The solvent was evaporated, and the residue was extracted with 50 ml. of acetone. The dried residue, 1.4 g., m.p. 255–262°, was shown by infrared to be predominantly α-amino-ε-caprolactam hydrochloride containing a small amount of pipecolic acid hydrochloride. Further dilution of the filtrate with acetone precipitated a second crop, 0.8 g., m.p. 180–190°, which the infrared spectrum indicated to be primarily pipecolamide hydrochloride with a small amount of pipecolic acid hydrochloride and a possible trace of lysine dihydrochloride. The acetone solution was evaporated to yield 4.2 g. (60% recovery) of unreacted chloro lactam, m.p. 91–93°. The products correspond approximately to a 45% yield of amino lactam and 26% yield of pipecolamide.

Ammonolyses of α-Chloro-ε-caprolactam in the Presence of Added Salts. (A) Evaluation of Salts.—The sodium, potassium, barium and calcium forms of Amberlite IRC-50[23] were prepared by slurrying the resin in aqueous media containing a large excess of the appropriate base. The filtered resin was washed with water and dried to constant weight in a vacuum oven at 110°. The equivalent capacity of each salt form, with respect to the bound metal ion, was determined by potentiometric titration with standard hydrochloric acid in 1 *N* aqueous potassium chloride.

The resin salts, and the various inorganic salts, were tested by heating with solutions of ammonium chloride in liquid ammonia. The reactions were carried out in a stainless-steel reactor on a rocking shaker. At the end of the specified reaction period, the reactor was cooled in a Dry Ice–methanol-bath, and the contents were filtered rapidly under slightly reduced pressure through a sintered glass funnel. The precipitate was washed with additional por-

(23) Rohm and Haas Co., Philadelphia, Pa.

(24) H. H. Fox, *J. Org. Chem.*, **17**, 542 (1952).

(25) W. A. Reckhow and D. S. Tarbell, THIS JOURNAL, **74**, 4960 (1952).

tions of liquid ammonia, and the combined filtrate was evaporated at room temperature under a stream of nitrogen. The residue was dried to constant weight and analyzed for its ammonia content.

In a typical experiment, 11.7 g. of dried Amberlite IRC-50 (K^+), with an equivalent capacity of 6 meq./g., was heated at 70° for 5 hr. with a solution of 4.3 g. of ammonium chloride in 240 ml. of liquid ammonia. The cooled mixture was filtered, and the precipitate was washed with 200 ml. of liquid ammonia. Evaporation of the filtrate left 1.4 g. of crystalline residue (dried to constant weight over phosphorus pentoxide). The residue analyzed for an ammonia content of 17.3%, corresponding to 0.76 g. (18% recovery) of ammonium chloride.

(B) Ammonolysis Reactions.—In a typical experiment, the 750-ml. reactor was charged with 44 g. (0.3 mole) of α-chloro-ε-caprolactam, 25 g. (0.18 mole) of potassium carbonate and 350 ml. (14.8 moles) of liquid ammonia. The mixture was heated with agitation at 85° for 24 hr. The reactor was cooled in a Dry Ice–methanol-bath, and the liquid ammonia was drawn off under suction through a sintered glass filter stick into a cooled trap. The insoluble residue was washed with two 50-ml. portions of liquid ammonia. The combined filtrates were evaporated, and the dried residue was dissolved in 65 ml. of absolute ethanol and filtered. The ethanol solution was diluted with additional solvent, concentrated under reduced pressure, and rediluted to a volume of 140 ml. Acidification by addition of ethanol saturated with hydrogen chloride resulted in precipitation of crystalline product which was collected and washed with acetone. The ethanol filtrate was evaporated, and the residue was extracted with acetone. The combined acetone-insoluble materials were dried to yield 21.8 g. (67.4% yield) of α-amino-ε-caprolactam hydrochloride, m.p. 289–293°. The infrared spectrum corresponded to that of an authentic sample[22] and showed no pipecolamide or other impurity to be present. This material burned to leave no ash, and analyzed correctly for the calculated chloride ion content of 21.5%.

The combined acetone extracts were evaporated under vacuum, and the dried residue was recrystallized from ligroin to yield 15 g. (34% recovery) of α-chloro-ε-caprolactam, m.p. 89–91°. Evaporation of the ligroin filtrate yielded 5.1 g. of sirupy residue. The infrared spectrum of this material indicated it to contain more than 50% unreacted α-chloro-ε-caprolactam.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF CHAS. PFIZER AND CO., INC.]

The Synthesis of 6-Chloropyridoxine. The Hydride Reduction of Pyridinedicarboxylic Acids

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6-Chloropyridoxine was synthesized *via* a six-step sequence from methyl acetopyruvate and cyanacetamide. The key step in this sequence was a novel reaction involving catalytic hydrogenation of a nitro group with simultaneous hydrolysis of an ester group and a nitrile group, but without simultaneous loss of a labile chloro group by hydrolysis or hydrogenolysis. Also of importance in the synthesis of 6-chloropyridoxine (and in related syntheses of pyridoxine studied coincidentally) was the hydride reduction of various substituted pyridinedicarboxylic acids to bis-(hydroxymethyl)-pyridines without prior esterification. Sodium borohydride—aluminum chloride in diethylene glycol dimethyl ether was found to be a system well suited for this purpose.

In connection with a broader study on the synthesis of potential antimetabolites, we have found occasion to synthesize a compound closely related in structure to vitamin B_6 (pyridoxine, XII). This compound is 6-chloropyridoxine (VIII). Although 6-chloropyridoxine has not shown any unusual activity in biological systems which would characterize it as an antimetabolite, the synthetic route by which it was obtained is of considerable interest. Thus the synthesis of 6-chloropyridoxine (and related syntheses of pyridoxine studied coincidentally) involve a surprising catalytic reduction–hydrolysis reaction. The syntheses also employ the hydride reduction of various pyridinedicarboxylic acids to bis-(hydroxymethyl)-pyridines without prior formation of esters. All of the intermediates and steps involved in these syntheses are outlined in the accompanying flow sheet.

The Synthesis of 6-Chloropyridoxine.—The first three steps in the synthesis of 6-chloropyridoxine—condensation of cyanacetamide with acetopyruvate ester, nitration of the pyridine so formed (I → II) and replacement of the hydroxyl by chlorine (II→ III)—were closely analogous to steps which have been carried out with the corresponding ethyl esters on at least three occasions in the past.[1–3] Only the first step of the sequence—condensation—was modified appreciably from the original processes[1] employed with the ethyl esters. Thus the sodium salt of methyl acetopyruvate was condensed directly with cyanacetamide without prior conversion of the former to free methyl acetopyruvate and without use of diethylamine as a catalyst.

With 2-methyl-3-nitro-4-carbomethoxy-5-cyano-6-chloropyridine (III) in hand, several synthetic routes to 6-chloropyridoxine (VIII) appear feasible. To summarize we might consider some possible transformations at individual positions in the pyridine ring

3-position	$-NO_2 \longrightarrow -NH_2 \longrightarrow -OH$
4-position[4]	$-COOCH_3 \longrightarrow -CH_2OH$ or
	$-COOCH_3 \longrightarrow -COOH \longrightarrow -CH_2OH$
5-position[4]	$-CN \longrightarrow -CH_2NH_2 \longrightarrow -CH_2OH$ or
	$-CN \longrightarrow -COOH \longrightarrow -CH_2OH$

Similar transformations have been carried out in the past,[1,2,5,6] but only with prior or simultaneous

(1) A. Itiba and S. Emoto, *Sci. Papers Inst. Phys. Chem. Research (Tokyo)*, **38**, 347 (1941).

(2) L. Velluz and G. Amiard, *Bull. soc. chim., France*, 136 (1947).

(3) R. G. Jones and E. C. Kornfeld, THIS JOURNAL, **73**, 107 (1951).

(4) Intermediates in which groups in the 4-position and 5-position are chemically bonded (*e.g.*, lactones, lactams, anhydrides, etc.) were not overlooked as possibilities. In any event, the basic transformations would remain essentially as outlined above.

(5) S. A. Harris and K. Folkers, THIS JOURNAL, **61**, 1245 (1939).

(6) J. H. Mowat, F. J. Pilgrim and G. H. Carlson, *ibid.*, **65**, 954 (1943).