Synthesis of ε-Caprolactam from Acetylene*

Sango KUNICHIKA and Yasumasa SAKAKIBARA**

(Kunichika Laboratory)

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The synthesis of ε-caprolactam from 1,4-butanediol or tetrahydrofuran was attempted by the following route, and the reaction conditions for every step were studied.

1,4-butanediol (I) or tetrahydrofuran (I′)⟶tetramethylene chlorohydrin (II)⟶tetramethylene chlorobrmide (III)⟶δ-chlorovaleronitrile (IV)⟶ethyl δ-chlorovalerate (V)⟶ethyl δ-cyanovalerate (IV)⟶ε-caprolactam

Methods for the preparation and the best yields of these substances were as follows, respectively.

II : by the reaction of I or I′ with hydrogen chloride; 80% (from I), 81% (from I′).

III : by the reaction of phosphorous tribromide or phosphor and bromine with crude II prepared from I′; 87% (with the former), 82% (with the latter), based on I′.

IV : by the reaction of III with potassium cyanide; 87% (conversion 96%).

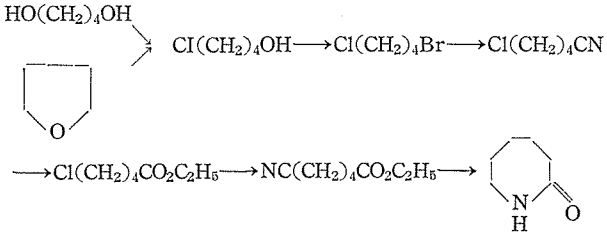
V : by the reaction of IV with alcoholic hydrogen chloride; 92%.

VI : by the reaction of V with potassium cyanide; 95%.

VII : by the cyclization (intramolecular aminolysis) of ethyl ε-aminocaproate prepared by the reduction of VI; 91%, based on VI.

The synthesis of ε-caprolactam from 1,4-butanediol or tetrahydrofuran has been attended to for the purpose of preparing nylon-6 from acetylene, since these materials have come to hand by Reppe's synthesis, and some related investigations have appeared. Reppe and coworkers[1] attempted to synthesize ε-caprolactam from tetrahydrofuran via valerolactone, and Shono and Hachihama[2] tried it from furfural via valerolactone. The synthesis[3,4] of ε-caprolactam from ethyl δ-cyanovalerate[5] or ε-aminocapronitrile[6], derived from tetrahydrofuran via adiponitrile, is also possible, and these methods have been patented. However, there are yet many problemical points in respect to the process from 1,4-butanediol or tetrahydrofuran.

In this investigation the following route for the synthesis of ε-caprolactam was adopted.



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** 国近　三吾，榊原　保正

Consequently, satisfactory results were obtained in each process of the reactions.

1. Preparation of Tetramethylene Chlorohydrin (TMCH) from 1,4-Butanediol (BD)

Sulfur monochloride[7], thionyl chloride[8] or hydrogen chloride[1,9] have been used as chlorinating agent. In the present work, hydrogen chloride was used, and a series of experiments was made to find optimum conditions for the reaction. The results are shown in Table 1.

TMCH : b. p. 79-81°/13 mm., n_D^{20} 1.4514, d_4^{20} 1.0878.

α-Phenylurethane, m. p. 53-54°.

Table 1. Preparation[a] of TMCH from BD.

Exp. No.	Reaction temp. (°C)	Reaction time (hr. min.)	Additives	Yield of products[b]				
				THF (%)	TMDC (%)	TMCH (%)	High boiling materials: 4,4'-DCDBE (crude) (g.)	High boiling materials: Recovered BD (crude) (g.)
1[c]	53- 56	7.20	None	2.5	Trace	27.6		22.6
2[c]	70- 72	5.05	〃	4.2	2.2	67.0		7.3
3[c]	73- 76	7.20	〃	2.5	5.4	79.5	1.7	
4	78- 82	5.30	〃	—	3.3	79.2	1.7	
5	78- 82	7.30	〃	—	6.8	71.5	1.7	
6	90-100	6.00	〃	—	16.9	52.5	3.2	
7[d]	88- 92	6.00	〃	11.1	6.6	61.1	1.7	
8	73- 74	7.30	Zinc chloride 5.0 g.	—	3.2	78.5	1.8	
9	73- 74	7.05	Sulfuric acid 3.0 ml.	—	3.5	69.4	1.7	
10[e]	73- 76	7.20	None	—	Trace	32.4		2.1

[a] BD : 45.0 g., Introducing rate of hydrogen chloride : about 41./hr.

[b] TMDC=Tetramethylene dichloride, 4,4'-DCDBE=4,4'-Dichlorodibutyl ether.

[c] The separation was made by direct fractionation under reduced pressure and in other cases by fractionation after neutralization and extraction.

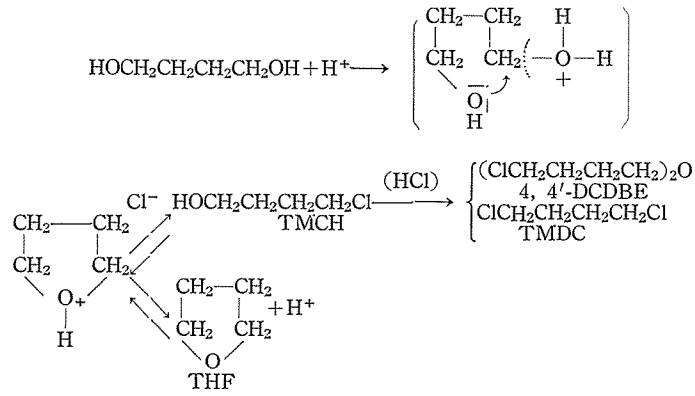
[d] The reaction was carried out with allowing low-boiling material (THF) formed to distil. From the distillate (7.5 g) THF (4.0 g.) was obtained.

[e] BD was treated with 60 ml. of conc. hydrochloric acid.

The formation of TMCH from BD was readier and more selective (optimum temp. 70-80°, yields 74-79%) than the formation of chlorohydrins from other polymethylene glycols[9,10]. This characteristic may be due to ready conversion of BD into tetrahydrofuran (THF) which reacts with hydrogen chloride to give TMCH. In fact, it was observed that the reacting mixture boiled at about 90° for a time in the first half of the period of reaction, owing to the formation of THF (Exp. Nos. 6, 7). It was also supposed that an equilibrium state,  $+HCl \rightleftharpoons Cl(CH_2)_4OH$, is attained in several hours of heating at 70-80°, and then the yields are no more increased by any longer duration of heat-

ing. The above conception is supported by the following facts: (1) TMCH decomposes readily into THF and HCl. (2) Similar treatment of a mixture of THF and H_2O (equimol. to THF) with hydrogen chloride gives TMCH in the same yield (Table 3, Exp. No. 4).

From the above observations the following mechanism may be presented for the reaction.



2. Preparation of TMCH from THF

TMCH has been prepared from THF by treating it with hydrogen chloride[11]. The reaction was studied, in consideration of the above results, to find favorable conditions for the preparation of TMCH. The results are shown in Tables 2 and 3. THF reacted with hydrogen chloride even at room temperature[1,12] to give

Table 2. Preparation[a] of TMCH from THF.

Exp. No.	Reaction temp. (°C)	Reaction time (hr. min.)	Hydrogen chloride (absorbed amt./ calcd.amt.)	Time of standing at room temp. after stopping of heating. (hr.)	Yield of products TMDC (%)	TMCH (%)	4,4'-DCDBE (%)
1	23-25[b]	8.50	1.59	40	Trace	70.4	4.8
2	41-43	9.00	1.59[c]	15	〃	73.0	4.6
3	51-55	9.20	1.53[c]	15	〃	76.9	4.0
4	19-22[b]	8.50	1.55	0	〃	26.7	2.8
5	41-44	10.30	1.45	〃	〃	55.2	4.2
6	58-63	6.30	1.31	〃	〃	76.7	5.0
7	62-67	7.00	1.30	〃	〃	80.5	5.4
8	60-75	8.40	1.31	〃	1.9	75.2	4.8
9	60-106[d]	5.50	1.10	〃	5.5	61.1	6.6
10[e]	60-65	7.00	1.42	〃	Trace	78.6	5.4

[a] THF: 36.0 g., Introducing rate of hydrogen chloride: about 4 l./hr.

[b] In an initial period of reaction, the temperature rised to about 40°C for a time.

[c] After heating was stopped, furthermore, hydrogen chloride was introduced at room temperature for about 1 hour.

[d] The preparation was made according to the procedure described in the Organic Syntheses.

[e] The separation was made by direct fractionation.

Table 3. Preparation[a] of TMCH from THF. Effect of additives.

Exp. No.	Reaction temp. (°C)	Reaction time (hr. min.)	Additives (g.)	Hydrogen chloride (absorbed amt./ calcd. amt.)	Yield of products TMDC (%)	TMCH (%)	4,4'-DCDBE (%)
1	60-65	6.40	Zinc chloride 1	1.37	Trace	79.8	7.0
2	55-65	7.40	Aluminium chloride 1	1.29	〃	73.6	5.4
3	62-70	6.20	Water 2	1.36(39%)[d]	1.2	81.0	3.0
4	60-71	7.20	Water 9	1.49(38%)	Trace	79.9	2.6
5[b]	68-70	7.00	Water(in aq. HCl)30	2.09(37%)	1.9	80.7	1.6
6[c]	69-71	7.00	Water(in aq. HCl)46	1.40(24%)	Trace	46.6	1.6

[a] THF: 36.0 g., Introducing rate of hydrogen chloride : about 4 l./hr.
[b] Hydrogen chloride was introduced into a mixture of 36% hydrochloric acid (40 ml.) and THF.
[c] THF was treated with 36% hydrochloric acid (60 ml.).
[d] Concentration (wt. %) of hydrogen chloride in the reaction mixture, calculated with regarding hydrogen chloride as unreacted.

TMCH, but a long duration was necessary to obtain TMCH in good yields (Table 2, Exp. Nos. 1, 4). On the other hand, at 60-70° good yields (77-80%) of TMCH were obtained in about 7 hours. This result was better than that of the ordinary procedure.

In the process of the formation of TMCH from THF, there is an equilibrium. Now, it was observed that the reverse reaction, i.e. the decomposition of TMCH proceeds slowly even at room temperature to a extent of 9%, as shown in

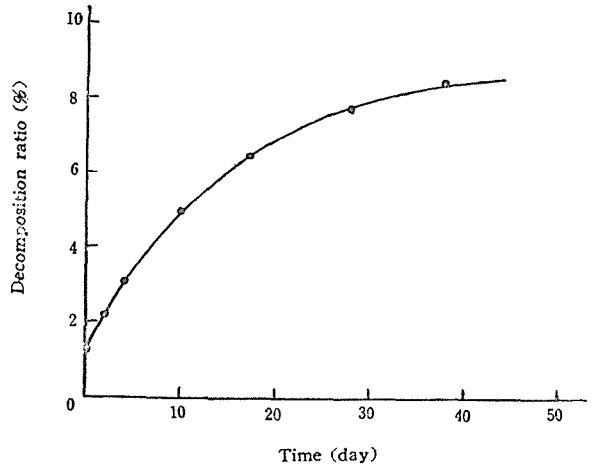


Fig. 1. Decomposition of TMCH (room temp.).
Hydrogen chloride formed was titrated with sodium hydroxide.

Fig. 1. Thus, the results of experiments may be interpreted by consideration based on the equilibrium, similarly as the case of the preparation of TMCH from BD.

3. Preparation of Tetramethylene Chlorobromide (TMCB)

TMCB was prepared by the action of phosphorous tribromide, or phosphor and bromine on crude TMCH, prepared from THF under the above optimum conditions and containing large amounts of hydrogen chloride, or purified TMCH. In the procedure of bromination, especially in the case of crude TMCH, the reactants were heated slowly after dropping of bromine or phosphorous tribromide, because retaining hydrogen chloride in the reaction medium for a longer period was supposed to give an advantage for the preparation (from the standpoint of existence of equilibrium : $THF+HCl \rightleftarrows Cl(CH_2)_4OH$). The results obtained with crude TMCH are shown in Table 4. This method of treatment gave much better yields (87% with phosphorous tribromide and 82% with phosphor and bromine, based on THF) than those of the ordinary method[13]. On the other hand, in the case where the reactants were heated relatively rapidly, the yield was inferior (Table 4, Exp. No. 3).

TMCB : b. p. 68-72°/20 mm., n_D^{20} 1.4882, d_4^{20} 1.4895.

Table 4. Preparation of TMCB from crude TMCH.

Exp. No.	Crude TMCH[a] (g.)(mole)	Brominating agent: Phosphor (used amt./calcd.amt.)	Brominating agent: Bromine (used amt./calcd.amt.)	Reaction temp. (°C)	Reaction time (hr. min.)	TMCB (%)
1	251 (2.0)	1.5 (31 g.)	1.7 (207 g.)	(Dropping of bromine) < 15	2.00[c]	82.2 (282 g.)
				−90	3.00[d]	
				90-95	2.30	
2[b] 628 (5.0)	188 (1.5)	Phosphoroustribromide 1.5 (203 g.)		< 15	0.40	87.1
				−90	3.20	
				90-95	3.00	
3	188 (1.5)	1.5	1.7	< 15	1.20	72.0
				−90	1.20	
				90-95	2.00	

[a] 628 g. of crude TMCH obtained from 360 g. (5.0 mole) of THF was divided into three parts and used.
[b] Phosphoroustribromide was dropped into crude TMCH.
[c] Dropping time of bromine.
[d] During this time the reactants was heated slowly to 90°.

4. Preparation of δ-Chlorovaleronitrile

This substance was prepared by the action of potassium cyanide on tetramethylene chlorobromide. A series of experiments was made to find suitable conditions for the preparation, using aqueous ethanol as solvent. The results are summarized in Table 5. As shown in Table 5, when the chlorobromide (40.0 g.) was heated with 1.5 times calculated amount of potassium cyanide in aqueous ethanol (ethanol 50 ml. and water 10-30 ml.) with stirring at about 60° for 6-8 hours, good results (conversion, 92-99% ; yields, 83-87%) were obtained.

δ-Chlorovaleronitrile : b. p. 78-80°/6 mm., n_D^{20} 1.4479, d_4^{20} 1.0577.

Table 5. Preparation[a] of δ-chlorovaleronitrile.

Exp. No.	Solvent Ethanol (ml.)	Solvent Water (ml.)	KCN (used amt./ calcd. amt.)	Reaction temp. (°C)	Reaction time (hr.)	Recovered chlorobromide (g.)	Conversion (%)	Yield of products[b] δ-Chlorovaleronitrile (g.)	(%)[c]	Adiponitrile (g.)	(%)[c]
1	50	10	1.5(22.7g.)	48-52	8.0	6.6	83.5	19.3	84.4	0.7	3.3
2	〃	〃	1.2	58-62	14.3	1.7	95.7	21.6	82.4	2.0	8.3
3	〃	〃	1.5	〃	8.0	0.5	98.8	22.3	82.5	1.8	7.2
4	〃	〃	2.0	〃	10.0	0	100	19.6	71.6	3.0	11.9
5	〃	〃	1.2	83-84(Rx)[d]	6.0	0.5	98.8	19.2	70.0	3.6	14.5
6	〃	5	1.5	58-62	8.0	6.5	83.7	19.9	86.8	0.8	3.8
3	〃	10	〃	〃	〃	0.5	98.8	22.3	82.5	1.8	7.2
7	〃	15	〃	〃	7.2	1.6	96.0	22.6	86.6	1.8	7.4
8	〃	30	〃	〃	6.0	3.1	92.2	22.0	87.1	1.0	4.3
9	30	40	〃	〃	7.0	12.8	68.0	15.9	85.4	0.5	2.9
10[e]	80	20	〃	〃	6.0	2.1	94.8	21.0	80.9	1.5	6.3

[a] Tetramethylene chlorobromide : 40.0 g.
[b] In Exp. No. 5, 1.5 g. of crude δ-bromovaleronitrile was obtained. In other cases its amount was very small.
[c] Calculated, based on the tetramethylene chlorobromide consumed.
[d] The reatcion was carried out under reflux.
[e] Acetic acid (0.5 ml.) was added in the reactants.

5. Preparation of Ethyl δ-Chlorovalerate

Ethyl δ-chlorovalerate was prepared by heating δ-chlorovaleronitrile under reflux with absolute ethanol into which dry hydrogen chloride was introduced. In connection with relative amounts of the reactants, Spiegel[14], who investigated the esterification of nitriles in the presence of sulfuric acid under anhydrous condition, has pointed out that at least 2 moles of alcohol and 1 mole of sulfuric acid for 1 mole of nitrile are necessary for direct esterification of nitriles. In consideration of this point the experiments were done under several different conditions. The results are shown in Table 6. The best yield was 92% (Exp. No. 5).

Ethyl δ-chlorovalerate : b. p. 78-81°/8 mm., n_D^{20} 1.4381, d_4^{20} 1.054.

Although the above esterification procedure has been generally used in organic

Table 6. Preparation of ethyl δ-chlorovalerate.

Exp. No.	Reactant δ-Nitrile (g.)	Reactant Ethanol (ml.)	Reactant HCl (g.)	Time of reflux (hr.)	Yield (g.)	Yield (%)	Residue (g.)
1	53.8	120(4.1)[a]	96[b](5.3)[a]	2.7	69.7	84.7	2.5
2	〃	〃	45 (2.5)	3.0	72.0	87.5	2.5
3	〃	〃	56 (3.1)	3.2	73.8	89.7	2.0
4	〃	150(5.2)	56 (3.1)	3.5	73.0	88.7	2.0
5	353	720(4.1)	342 (3.1)	6.0	455	92.2	6.5

[a] The molecular ratio of ethanol and hydrogen chloride to the δ-nitrile.
[b] Saturated with hydrogen chloride.

synthesis and iminoester hydrochloride has been postulated as an intermediate in the formation of ester[15], the stoichiometric relations of the reaction have not yet clarified. From the standpoint of the following results, the present authors offer some informations on the reaction. Besides ethyl δ-chlorovalerate (87.4% yield) and ammonium chloride (97.3%), ethyl chloride (b. p. 14-15°, confirmed as propioanilide, m. p. 103-4°) was also obtained by heating δ-chlorovaleronitrile with alcoholic hydrogen chloride under reflux for 3 hours and it amounted to the molecular ratio of 0.82 to 1 of δ-chlorovaleronitrile. On the other hand, in the absence of δ-chlorovaleronitrile, the amount of ethyl chloride, formed by the reaction of ethanol with hydrogen chloride, was much smaller, as shown in Fig. 2. From the above results the reaction formula may be supposed to be as follows:

$$RCN+2R'OH+2HCl=RCO_2R'+R'Cl+NH_4Cl$$

where $R=Cl(CH_2)_4-$, $R'=C_2H_5-$.

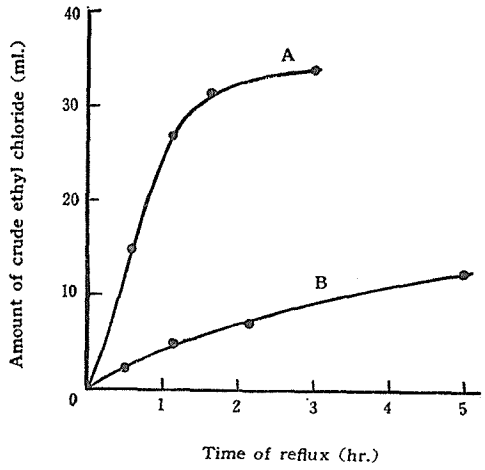


Fig. 2. Formation of ethyl chloride.
A : δ-Chlorovaleronitrile 58.8 g., ethanol 120 ml., hydrogen chloride 48 g.
B : Ethanol 120 ml., hydrogen chloride 43.5 g.

Furthermore, for the formation of ester (III) from iminoester hydrochloride

$$RCN+R'OH+HCl\longrightarrow RC(=NH\cdot HCl)OR' \quad (I) \qquad (1)$$

$$RC(=NH_2Cl^-)OR' \quad (I) \xrightarrow{R'OH,\ HCl} RCONH_2 \quad (II) + R'Cl \longrightarrow RCO_2R' + NH_4Cl \quad (III) \qquad (2\text{-}1)$$

$$RC(=NH_2Cl^-)OR' \quad (I) \xrightarrow{R'OH} RC(-NH_3Cl^-)(OR')_2 \quad (IV) \xrightarrow{HCl} RCO_2R + NH_4Cl + R'Cl \quad (III) \qquad (2\text{-}2)$$

(2)

(I) the above two reaction schemes (2-1) and (2-2) may be postulated.
The reaction scheme (2-1) is supported by the fact that iminoester hydrochlorides decompose generally into amides and alkyl chlorides by heating[16]. In fact, amide (II) (m. p. 77-78°) was obtained in 7.6% yield besides ethyl δ-chlorovalerate (74.0%) when δ-chlorovaleronitrile was heated with alcoholic hydrogen chloride for 50 min. Also, it has been ascertained by McElvain et al.[17] that in the case of formation of orthoesters by the reaction of iminoester hydrochlorides with alcohols, the decomposition of iminoester hydrochlorides into amides and alkyl chlorides proceeds competitively and its decomposition becomes vigorous with the elevation of the reaction temperature. Since the above both reactions are a competitive reaction, it seems probable that the esterification proceeds also via (IV) which is postulated as an intermediate[18] in the formation of orthoesters from iminoester hydrochlorides, as shown in the scheme (2-2).

6. Preparation of Ethyl δ-Cyanovalerate

This substance was prepared by the action of potassium cyanide on ethyl δ-chlorovalerate. The results are listed in Table 7. In cases where ethanol was used as solvent, ethyl δ-cyanovalerate was obtained in fairly good yields only when the reaction was carried out at high temperature (130-140°) in an autoclave (Exp. Nos. 4, 5). Dimethylformamide was a favorable solvent. By dropping ethyl δ-chlorovalerate slowly into a heated mixture of dimethylformamide and potassium cyanide and heating the mixture for 3 hours (called Dropping method), ethyl δ-cyanovalerate was isolated in 100% conversion and 94.5% yield (Exp. No. 9).

Ethyl δ-cyanovalerate: b. p. 108-110°/5 mm., n_D^{20} 1.4324, d_4^{20} 0.9933.

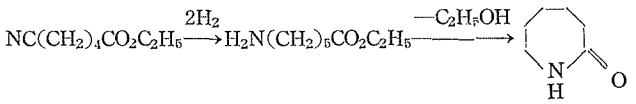
Table 7. Preparation[a] of ethyl δ-cyanovalerate.

Exp. No.	Solvent[b] (ml.)	KCN (g.)	Reaction temp. (°C)	Reaction time (hr.)	Recovered δ-chlorovalerate (g.)	Conversion (%)	Yield (g.)	Yield (%)[c]	Remark
1	E 50-W 7	33(2.1)[d]	84[e]	17.0	11.5	71.3	15.4	57.3	
2	E 25-EG 25	23.7(1.5)	97[e]	7.0	2.5	93.8	20.5	58.0	
3	E 100	〃	113-118	8.0	25.4	36.5	11.0	80.0	350 ml. autoclave was used.
4	E 70	〃	130-135	8.0	9.1	77.3	25.3	86.8	
5	〃	〃	130-140	13.0	5.3	86.8	28.5	87.2	
6	DFA 70	〃	155-158[e]	6.5	5.8	85.5	28.8	89.4	Mixing mehod
7	〃	〃	〃	9.5	1.7	95.7	33.1	91.8	
8	〃	〃	〃	5.0(2.0)[f]	0	100	34.8	92.4	Dropping method
9	〃	〃	〃	3.0(2.0)	0	100	35.6	94.5	

[a] Ethyl δ-chlorovalerate: 40.0 g.
[b] E=Ethanol, W=Water, EG=Ethylene glycol, DFA=Dimethyl formamide.
[c] Calculated, based on the ethyl δ-chlorovalerate consumed.
[d] 2.1 times calculated amount was used.
[e] Under reflux.
[f] Dropping time of ethyl δ-chlorovalerate.

7. Preparation of ε-Caprolactam

ε-Caprolactam was synthesized by the reduction of ethyl δ-cyanovalerate to ethyl ε-aminocaproate and the cyclization (intramolecular aminolysis) of the latter.



(2)

The cyclization has been made by heating ethyl ε-aminocaproate. The heating, however, in the absence of solvent has been reported by some workers[19] to give its polymer mainly and ε-caprolactam in poor yields. Recently, two methods has been patented for the preparation of ε-caprolactam from ethyl δ-cyanovalerate without isolating ethyl ε-aminocaproate. In the one method[20], after the reduction the reducing catalyst was removed off, and then the cyclization process has been carried out at 200–230°C in a closed vessel using large amounts of solvents (in the following description, called this method double process method). In the other[21], the cyclization has been tried successively without the removal of the catalyst (called single process method). But the single process method has given lower yields of ε-caprolactam than those of the double process method. This is supposed to be chiefly due to side reactions[22,23] which are induced at high temperature by the action of reducing catalyst; the alkylation of amines by amines (reaction 3) and in cases where alcohols were used as solvent the alkylation of amines by alcohols (reaction 4).

$$2RNH_2 \longrightarrow RNHR + NH_3 \quad (3)$$

$$RNH_2 + R'OH \longrightarrow RNHR' + H_2O \quad (4)$$

where $R = -(CH_2)_5CO_2C_2H_5$.

In the ammonolysis[24] and aminolysis[25] of esters, certain glycols and related compounds have been found by Day and coworkers to have a notable, catalytic effect. At first the present authors tried the cyclization by means of the single and double process methods using ethylene glycol or several others as solvent. Consequently, favorable conditions for the single process method were found. Next, since it was ascertained that ethylene glycol accelerated notably the cyclization reaction, a method of dropping ethyl ε-aminocaproate into heated ethylene glycol was attempted with the intention of suppressing intermolecular aminolysis of ethyl ε-aminocaproate. This method gave good results even when relatively small amounts of ethylene glycol were used.

Procedures and results are as follows.

a) Reduction and cyclization. i) Single process method. In a 350 ml. autoclave were placed ethyl δ-cyanovalerate, solvent and Raney nickel catalyst. The autoclave was then swept out with hydrogen and anhydrous liquid ammonia was added through a short introducing tube, after taking its specified amount in a small metallic vessel (50 ml.) fitted with a needle valve. The autoclave was charged with hydrogen and heated with shaking.

ii) Double process method. A 350 ml. autoclave was charged with reactants

as the above manner and was heated at 90-120° for 1-1.5 hours with shaking. The absorption of hydrogen ceased practically in 30 minutes. After cooling, Raney nickel was filtered off and the filtrate was heated with stirring in the autoclave at higher temperature again.

iii) Dropping method. The reduction procedure was the same as above (ii). After removal of Raney nickel, ethanol was distilled off under reduced pressure. The residue, crude ethyl ε-aminocaproate, was dropped into ethylene glycol heated at a specified temperature, and the mixture was keeped at the temperature under stirring. During the reaction period, ethanol formed by the cyclization reaction was allowed to distil off.

b) Separation of products. The reaction mixture was filtered and the solvent was distilled off under atmospheric or reduced pressure, and the residue was fractionated.

Ethyl ε-aminocaproate: b. p. 80-83°/3 mm., n_D^{20} 1.4430, d_4^{20} 0.952.

ε-Caprolactam: b. p. 106-109°/3 mm., m. p. 68-69° (from tetrahydrofuran).

Anal. Found : C, 63.82%; H, 9.78%.

Table 8. Relation between reaction temperature and yield[a].

Exp. No.	δ-Cyano-valerate	Solvent[b]	NH_3	Reduction		Cyclization		Yield of products				Total yield	Residue
				Temp.	Time	Temp.	Time	Amino-caproate		Lactam			
	(g.)	(ml.)	(g.)	(°C)	(hr.)	(°C)	(hr.)	(g.)	(%)	(g.)	(%)	(%)	(g.)
1	30	E 120	11			93-104	1.4	25.2	81.9	2.0	9.1	91.0	2.0
2	15	〃 135	6			160-167	3.7	7.5	49	3.8	35	84	2.3
3	〃	〃	9			193-200	3.4	(3.0)[c]		5.5	50		5.2
4	〃	〃	8			230-235	2.0	(2.9)[d]		5.0	46		6.1
5	〃	t-B 135	9			222-225	3.0	2.6	17	6.4	58	75	2.7
6	30	THF 110	0			125-130	3.0	22.3	72.5	1.0	4.6	77.1	6.6
7	15	〃 135	5			220-225	3.3	1.3	8.4	7.4	68	76	2.3
8	〃	EGMME 135	9			119-122	4.0	8.7	57	3.5	32	89	1.9
9	〃	〃	5.5			145-152	4.0	5.9	38	5.3	48	86	2.5
10	〃	〃	8			200-202	2.2	0.3	2	7.9	72	74	5.2
11	〃	EG 135	7			108-113	4.0	?		7.2	66		3.6
12	〃	〃	7			132-137	4.0	?		7.7	70		3.6
13	〃	〃	8			150-155	3.5	?		8.0	73		3.1
14	〃	〃	7			175-179	2.0	?		7.8	71		4.2
15	〃	E 135	7	100-120	1.5	200-203	3.7	4.1	27	6.9	63	90	1.6
16	〃	〃	8	89-105	1.2	230-237	3.6	1.0	6.5	8.2	75	82	3.2
17	〃	THF 135	8	89-107	1.5	235-240	3.5	0.6	4	9.0	82	86	1.8
18	〃	〃	8	85-115	1.5	250-255	4.8	0		8.8	80	80	1.9
19	〃	EGMME 135	10	92-104	1.0	190-195	2.5	2.0	13	7.8	71	84	1.8

[a] Raney nickel ethanol paste: 3 g., Initial pressure of hydrogen: 60-75 atm. (room temp.). Experiments 1-14 were made by the single process method and the others by the double process method.

[b] E=Ethanol, t-B=tert.-butanol, THF=Tetrahydrofuran, EGMME=Ethylene glycol monomethyl ether, EG=Ethylene glycol.

[c] b.p. 77-80°/2 mm., n_D^{20} 1.4511, d_4^{20} 0.939.

[d] b.p. 77-81°/2 mm., n_D^{20} 1.4620, d_4^{20} 0.962

Calcd. for $C_6H_{11}NO$: C, 63.68%; H, 9.80%.

In some cases, noted in Table 10 and 12, the above filtrate was diluted with 50 ml. of saturated sodium chloride solution and extracted 6 times with 80 ml. of chlorofofm. The combined extracts were washed with 20 ml. of sodium chloride, dried over anhydrous magnesium sulfate and fractionated.

c) Results. i) Solvent and reaction temperature. Ethanol, tert.-butanol, tetrahydrofuran, ethylene glycol monomethyl ether and ethylene glycol were used as solvent. The results are listed in Table 8. Among these solvents, ethylene glycol accelerated most notably the cyclization reaction, followed by ethylene glycol monomethyl ether, and ethanol, tert.-butanol and tetrahydrofuran in that order. With ethylene glycol the cyclization proceeded considerably rapidly even at about 110°, but the yield of ε-caprolactam was unsatisfactory. In cases of the other solvents the higher temperatures were necessary. In cases where the cyclization was carried out in ethanol at high temperature by the single process method, ε-caprolactam was obtained not only in lower yields, but also contaminated with an uncertain fraction (Table 8, Note c, d) which may be a mixture of ethyl ε-aminocaproate, ethyl N-ethyl-ε-aminocaproate (formed by reaction 4) and N-ethyl-ε-caprolactam[26]. On the other hand, in the case of tert.-butanol which has not an action of N-alkylation of amines[23], the fraction of ethyl ε-aminocaproate was pure. In Exp. No. 6 where ammonia was not added, 5,5′-diethoxycarbonylpentylamine (4.4 g.), colorless liquid, was obtained by further fractionation of the residue (6.6 g.).

5,5′-diethoxycarbonylpentylamine hydrochloride, m. p. 162-4°.

Anal. Found : N, 3.90%.

Calcd. for $C_{16}H_{32}O_4NCl$: N, 4.14%.

ii) Relation between amount of solvent and yield. Experiments were tried by the double process method using various amounts of tetrahydrofuran. The results are listed in Table 9. From the results it was assured that larger amounts of solvent are favorable for the reaction.

iii) Effect of ammonia. Since ethylene glycol accelerates ammonolysis in addition to aminolysis of esters, ethyl ε-aminocaproate (and ε-caprolactam) may undergo partly ammonolysis by ammonia in the course of cyclization, especially

Table 9. Relation between amount of solvent and yield[a].

Exp. No.	Tetrahydrofuran (ml.)	Reaction temp. (°C)	Reaction time (hr)	Yield of prducts: Aminocaproate (g.)	Aminocaproate (%)	Lactam (g.)	Lactam (%)	Total yield (%)	Residue (g.)
20[b]	70	230-240	3.8	0.3	2	8.0	73	75	3.0
17	135	235-240	3.5	0.6	4	9.0	82	86	1.8
21	200	240-243	3.5	Trace		9.4	86	86	1.7

[a] Ethyl δ-cyanovalerate : 15.0 g. The reduction procedure: see Note b and Exp. No. 17 in Table 8.

[b] The reduction conditions were similar to those for Exp. No. 17 except that 30 g. of ethyl δ-cyanovalerate were used. The half amount of the resulting solution was used in Exp. No. 20 and the rest in Exp. No. 21, respectively.

in cases where ethylene glycol was used as solvent. The results obtained by the single process method using ethylence glycol and various amounts of ammonia are shown in Table 10. As expected, the yields of ε-caprolactam were decreased by larger amounts of ammonia. In Exp. No. 25, ε-aminocaproamide (2.7 g., 21%), b. p. 152-8°/2 mm., m. p. 47-50° (from THF, confirmed as ε-benzoylaminocaproic acid, m. p. 75-8°), was obtained from the residue (6.5 g).

Table 10. Effect of ammonia[a].

Exp. No.	NH_3 (g.)	Reaction temp. (°C)	Reaction time (hr.)	Yield of products: Amino-caproate (g.)	Lactam (g)	Lactam (%)	Residue (g.)
22[b]	0	129-132	3.0	0	7.2	66	2.2
23	0	128-130	3.0		7.9	72	3.8
24	3.5	128-131	3.0		8.4	77	2.8
12	7	132-137	4.0		7.7	70	3.6
25	26	130-134	3.0		5.5	50	6.5

[a] Ethyl δ-cyanovalerate: 15.0 g., Ethylene glycol: 135 ml., Raney nickel ethanol paste : 3 g., Initial pressure of hydrogen: 50-70 atm.
[b] The separation was worked up by extraction and fractionation.

Table 11. Use of mixed solvents.[a]

Exp. No.	Solvent (ml.)		NH_3 (g.)	Reaction temp. (°C)	Reaction time (hr.)	Yield of Lactam (g.)	Yield of Lactam (%)	Residue (g.)
26	EG35-E	100	4	140-144	2.8	9.0	82	2.4
27	〃 70-t-B	65	8	149-155	6.0	9.0	82	2.6
28	〃 40-〃	95	7	149-155	6.0	9.2	84	2.6
29	〃 70-THF	65	7	148-153	6.0	9.1	83	2.6
30	〃 35-〃	100	5	145-146	3.3	9.0	82	2.6
31	〃 35-〃	100	4.5	144-148	5.0	9.1	83	2.4
32	〃 35-NGMME	100	4	127-133	3.0	8.9	81	2.5
33	〃 35- 〃	100	4	145-146	2.0	9.4	86	2.4

[a] Ethyl δ-cyanovalerate: 15.0 g., Raney nickel ethanol paste: 3 g., Initial pressure of hydrogen: 50-70 atm.

iv) Mixed solvent. A series of experiments was made by the single process method at 130-155° using mixed spolvents consisting of ethylene glycol and ethanol, tert.-butanol, tetrahydrofuran or ethylene glycol monomethyl ether in volume ratio of 1 to 1-3. As shown in Table 11, better results were obtained than those of ethylene glycol alone.

v) Dropping method. Dropping at a suitable rate of ethyl ε-aminocaproate into heated ethylene glycol may be expected to diminish the losses caused by intermolecular aminolysis of ethyl ε-aminocaproate, because the cyclization proceeds rapidly in ethylene glycol, as described above. The results are listed in Table 12. This method gave better yields (88-91%) than those of the other methods, and the yields were not lowered even if considerably small amounts

Table 12. Dropping method.

Exp. No.	Cyano-valerate (g.)	Reduction[a] Ethanol (ml.)	Temp. (°C)	Time (hr.)	Cyclization Ethylene glycol (ml.)	Temp. (°C)	Time (hr.)		Yield of prducts Amino-caproate (g.)	Lactam (g)	(%)	Residue (g.)
34[d]	30	130	87–103	1.0	100	156–160	5.2[b]	(3.0)[c]	0	19.3	88.2	1.5
35	30	120	103–112	1.0	100	161–165	4.3	(3.2)		19.6	89.5	3.1
36[d]	30	120	85–101	1.1	100	178–183	2.6	(1.5)	0	18.3	83.6	1.9
37	30	130	109–115	1.2	60	180–185	4.2	(2.7)		20.0	91.3	3.4
38	30	130	91–105	1.4	40	185–188	4.4	(3.1)		19.3	88.2	3 4
39	ethyl ε-amino-caproate 12.2	—	—	—	50	128–135	4.0	(1.3)		7.6	88	1.2

[a] Raney nickel ethanol paste : 3 g., Ammonia : 8–9 g., Initial pressure of hydrogen : 87–90 atm.

[b] Total reaction time.

[c] Dropping time.

[d] The separation was worked up by extraction and fractionation.

of ethylene glycol was used, but high temperature was employed. For example, even when the volume ratio of ethylene glycol to ethyl δ-cyanovalerate was 4 to 3, a satisfactory yield (88.2%) was obtained at about 185° (Exp. No. 38).

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