Synthesis of DL*-Lysine from 1, 1, 1, 5-Tetrachloropentane*

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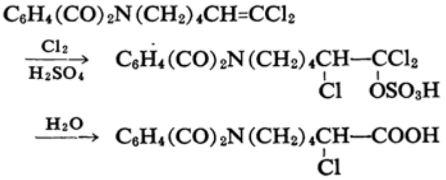
In a previous paper[1], the synthesis of DL-lysine from 1, 1, 1, 5-tetrachloropentane which was prepared by the telomerization of ethylene and carbontetrachloride via benzoylaminocaproic acid as the intermediate was reported.

The present work is concerned with another process for the synthesis of DL-lysine from 1, 1, 1, 5-tetrachloropentane involving seven steps as shown below.

$$\begin{array}{l}
\underset{\text{(I)}}{Cl(CH_2)_4CCl_3} \longrightarrow \underset{\text{(II)}}{Cl(CH_2)_3CH{=}CCl_2} \\
\longrightarrow \underset{\text{(III)}}{CN(CH_2)_3CH{=}CCl_2} \longrightarrow \underset{\text{(IV)}}{H_2N(CH_2)_4CH{=}CCl_2} \\
\longrightarrow \underset{\text{(V)}}{C_6H_4(CO)_2N(CH_2)_4CH{=}CCl_2} \\
\longrightarrow \underset{\text{(VI)}}{C_6H_4(CO)_2N(CH_2)_4CHCl\text{-}COOH} \\
\longrightarrow \underset{\text{(VII)}}{C_6H_4(CO)_2N(CH_2)_4CHNH_2\text{-}COOH} \\
\longrightarrow \text{DL-Lysine}\cdot HCl
\end{array}$$

In the first step, I was dehydrochlorinated to 1, 1, 5-trichloropentene-1 (II) in the presence of anhydrous ferric chloride as the catalyst[2]. Since the dichlorovinyl group in II is inert towards nucleophilic reagents, II was treated with potassium cyanide in dimethylformamide (DMF) solution to prepare 1, 1-dichloro-5-cyanopentene-1 (III). In the hydrogenation of III under a high pressure of hydrogen, the Raney cobalt was found to be a favorable catalyst for attacking the nitrile group selectively. 1, 1-Dichloro-6-aminohexene-1 (IV) was acylated by heating with phthalic anhydride to give 1, 1-dichloro-6-phthaliminohexene-I (V).

Some examples of the reaction between the dichlorovinyl group and chlorine in a sulfuric acid solution to obtain α-chlorocarboxylic derivatives were reported by Russian authors[3]. The reaction mechanisms are explained as follows.



$$\begin{array}{l}
C_6H_4(CO)_2N(CH_2)_4CH{=}CCl_2 \\
\xrightarrow[H_2SO_4]{Cl_2} C_6H_4(CO)_2N(CH_2)_4\underset{Cl}{CH}-\underset{OSO_3H}{CCl_2} \\
\xrightarrow{H_2O} C_6H_4(CO)_2N(CH_2)_4\underset{Cl}{CH}-COOH
\end{array}$$

A chlorine atom and a sulfuric acid residue are added to the double bond of V, and the resulting adduct decomposes with water to give 2-chloro-6-phthaliminocaproic acid (VI). The resulting VI was aminated with aqueous ammonia. Since phthaliminolysine could not be crystallized, the reaction mixture was concentrated, and without further purification it was hydrolyzed by hydrochloric acid to give DL-lysine. DL-Lysine monohydrochloride was separated and purified as in the previous paper[1].

Experimental

1, 1, 5-Trichloropentene-1 (II).—Dehydrochlorination of I was investigated using several Friedel-Crafts type catalysts. After the evolution of hydrogen chloride had ceased, the reaction mixture was

TABLE I. DEHYDROCHLORINATION OF 1, 1, 1, 5-TETRACHLOROPENTANE

$Cl(CH_2)_4CCl_3$ g.	Catalyst g.	Temp. ×Time °C×hr.	$Cl(CH_2)_3\cdot CH{=}CCl_2$ g.	Unreacted $Cl(CH_2)_4CCl_3$ g.	Yield* %
126	$ZnCl_2$ 3.0	120×4	26.0	69.0	83
126	$AlCl_3$ 2.0	60×2	85.0	8.0	87
126	$SnCl_4$ 3.0	130×3	37.5	76.0	91
210	$FeCl_3$ 3.0	55×3	148.0	10.0	90
420	$FeCl_3$ (6+2)**	55×3	318.0	—	92

* The yield was calculated taking the recovered tetrachloropentane into account.

** The catalyst was added in two portions 2 g. of ferric chloride was added after 2 hr. reaction.

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[1] K. Saotome, *J. Chem. Soc. Japan, Ind. Chem. Sec.* (*Kogyo Kagaku Zasshi*), **65**, 1061 (1962).

[2] A. N. Nesmeyanov and L. I. Zakharkin, *Izv. Akad. Nauk SSSR, Otd. Khim. Nauk*, **1951**, 505; A. N. Nesmeyanov et al., ibid., **1955**, 657.

[3] A. N. Nesmeyanov, V. N. Kost and R. Kh. Freidlina, *Dakl. Akad. Nauk SSSR*, **103**, 1029 (1955).

TABLE II. HYDROGENATION OF 1,1-DICHLORO-5-CYANOPENTENE-1

$CN(CH_2)_3CH=CCl_2$ g.	(mol.)	Catalyst	g.	EtOH ml.	NH_3 g.	H_2 kg./cm²	Temp. ×Time °C hr.	$H_2N(CH_2)_4CH=CCl_2$ g.	%
33.0	(0.2)	Co	3.0	100	12.5	80	80×6	16.5	49.1
33.0	(0.2)	Co	3.0	100	satu.	85	80×5	17.4	51.8
33.0	(0.2)	Co	6.0	200	16.0	80	80×3	19.0	56.0
33.0	(0.2)	Co	6.0	100	satu.	80	80×5	19.8	58.8
33.0	(0.2)	Ni	3.0	100	10.0	80	80×3	7.8	22.9

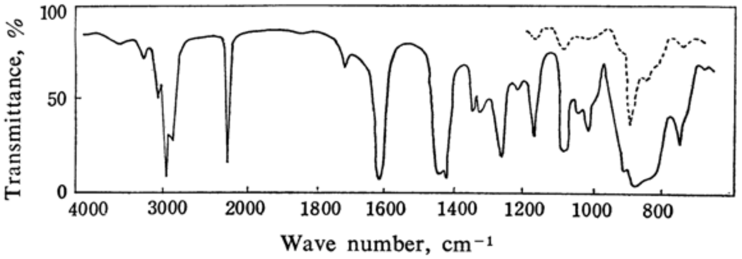

Fig. I. Infrared spectrum of 1,1-dichloro-5-cyanopentene.

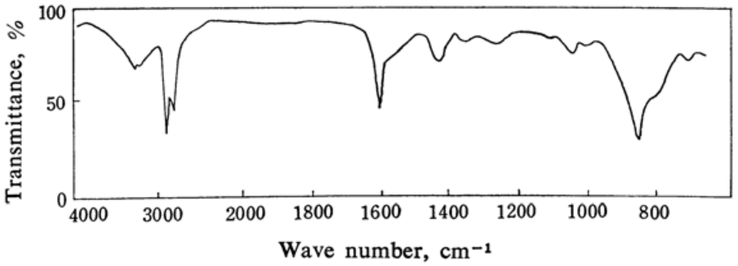

Fig. 2. Infrared spectrum of 1,1-dichloro-6-aminohexene.

washed with water, then distilled under reduced pressure to afford II, b. p. 48∼50°C/4 mmHg, n_D^{20} 1.4892 (lit. b. p. 68∼69°C/7 mmHg, n_D^{20} 1.4892). The reaction conditions and the yields are shown in Table I.

When aluminum chloride which is a stronger catalyst than ferric chloride was used for the reaction, the reaction proceeded smoothly at a lower temperature. But the resinous by-product was observed to increase in the distillation residue.

However, in the case of a weaker catalyst such as zinc chloride or stannic chloride, the reaction proceeded only slowly even at an elevated temperature. The best result was obtained when ferric chloride was added in two portions. The infrared spectrum of II showed a strong absorption band at 1620 cm⁻¹ due to C=C double bond.

1,1-Dichloro-5-cyanopentene-1 (III).—Into a solution of 82 g. of potassium cyanide in 500 ml. of DMF maintained at 115°C was added dropwise 174 g. of II over one hour with stirring. The reaction was continued for additional two hours. Potassium chloride was filtered and the solvent was evaporated under reduced pressure. Distillation of the residue under reduced pressure afforded 142 g. of III (88% yield), b. p. 99∼101°C/5 mmHg, n_D^{20} 1.4818 (lit.[4] b. p. 80∼81°C/3 mmHg, n_D^{20} 1.4815).

1,1-Dichloro-6-aminohexene-1 (IV).—Hydrogenation of III was carried out using the Raney cobalt and nickel (prepared according to the recipe W-7[5]) as a catalyst in an alcoholic solution containing ammonia. An autoclave (500 ml.) equipped with a magnetic stirrer was used for the reaction. After removal of the catalyst and the solvent, the reaction product was washed with water and extracted with ether. Distillation of the extract under reduced pressure afforded IV, b. p. 77∼80°C/5 mmHg, n_D^{20} 1.4860. Details of the reaction are shown in Table II.

From Table II, the Raney cobalt is shown to be the preferable catalyst to the Raney nickel for the selective hydrogenation of III. On the other hand, the hydrogenation of 1,1,5-trichloropentene-1 was attempted under the same conditions, but no absorption of hydrogen was observed. An attempt to hydrogenate the nitrile group in III by metallic sodium in an alcoholic solution was also made. But the product was resinous, and no IV was obtained.

Infrared Spectra.—The spectra of III and IV are shown in Figs. 1 and 2. The characteristic band

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4) A. N. Nesmeyanov, L. I. Zakharkin and R. Kh. Freidlina, *Izv. Akad. Nauk SSSR, Otd. Kim. Nauk*, **1954**, 34.

5) H. Adkins and H. R. Billica, *J. Am. Chem. Soc.*, **70**, 695 (1948).

at 2220 cm^{-1} due to cyano group in Fig. 1 disappears in Fig. 2, and a new band at 3250 cm^{-1} (NH) appears in Fig. 2. While the band at 1620 cm^{-1} assigned to carbon-carbon double bond is observed both in Fig. 1 and Fig. 2.

1, 1-Dichloro-6-phthaliminohexene-1 (V).—A mixture of IV (16.4 g.) and phthalic anhydride (29 g.) was heated under nitrogen atomosphere at 145~150°C in an oil bath for 4 hr. Aqueous solution of sodium hydroxide (5%, 120 ml.) was poured to the reaction mixture to dissolve the excess phthalic anhydride. The precipitate was separated, powdered and washed several times with water. Its recrystallization from ethanol afforded white crystals. Yield, 27.4 g. (96%) ; m. p., 56°C.

Found : C, 56.56 ; H, 4.70 ; N, 4.59. Calcd. for $C_{14}H_{13}O_2NCl_2$: C, 56.39 ; H, 4.39 ; N, 4.70%.

2-Chloro-6-phthaliminocaproic Acid (VI).—Into 70 ml. of sulfuric acid (96%) cooled with ice-water, V (15 g.) was added slowly to make a clear solution. Chlorine gas was passed through this solution at 5°C with stirring. The reaction was continued for 3 hr. until the evolution of hydrogen chloride had ceased. The reaction mixture was poured into ice-water, and the solidified product was washed with water. Recrystallization from benzene afforded white crystals. Yield, 14.1 g. (95%) ; m. p., 124~125°C.

Found : C, 56.83 ; H, 4.72 ; N, 5.01. Calcd. for $C_{14}H_{14}O_4NCl$: C, 56.82 ; H, 4.73 ; N, 4.73%.

DL-Lysine Monohydrochloride.—Into an autoclave (200 ml.) equipped with a magnetic stirrer, were taken VI (10 g.), ammonium carbonate (15 g.) and 100 ml. of 28% aqueous ammonia. The reaction was carried out at 60~65°C for 8 hr. The reaction mixture was concentrated to about 30 ml. to remove free ammonia. To this solution was added 80 ml. of 20% hydrochloric acid and the mixture was refluxed for 12 hr. Phthalic acid precipitated was filtered off and the solution was concentrated to dryness under reduced pressure. The solid product was dissolved in 200 ml. of water. The solution was treated with anion exchange resin (Amberlite IR-4B) to remove the excess hydrochloric acid. The solution was concentrated and cooled. DL-Lysine monohydrochloride was precipitated by adding acetone. The pure sample (3.3 g.) was obtained by recrystallization from an acetone-water mixture. The yield was 53.4% of the theoretical amount. This was identified by paper chromatography with the authentic sample and shown to be one-spot.

Found : C, 39.21 ; H, 8.06 ; N, 15.46. Calcd. for $C_6H_{15}O_2N_2Cl$: C, 39.45 ; H, 8.23 ; N, 15.34%.

Summary

DL-Lysine was synthesized from 1, 1, 1, 5-tetrachloropentane. The process involves seven steps ; 1, 1, 5-trichloropentene-1 (92%), 1, 1-dichloro-5-cyanopetene-1 (88%), 1, 1-dichloro-6-aminohexene-1 (59%), 1, 1-dichloro-6-phthaliminohexene-1 (96%), 2-chloro-6-phthaliminocaproic acid (95%), DL-lysine monohydrochloride (53%). The over-all yield from 1, 1, 1, 5-tetrachloropentane to DL-lysine monohydrochloride was 23%.

In the hydrogenation of 1, 1-dichloro-5-cyanopentene-1 to 1, 1-dichloro-6-aminohexene-1; the Raney cobalt was found to be a favorable catalyst for attacking the nitrile group selectively.

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