Synthesis of DL-*Glutamic Acid from 1, 1, 1, 5-Tetrachloropentane*

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Various amino acids have been synthesized by Russian authors using ethylene-carbon tetrachloride telomers as the starting raw materials. In the previous papers,[1,2] the present authors have reported on the synthesis of DL-lysine from 1, 1, 1, 5-tetrachloropentane which had been prepared by the telomerization of ethylene and carbon tetrachloride. This paper presents a novel way for the synthesis of DL-glutamic acid from 1, 1, 1, 5-tetrachloropentane. The process involves the five steps shown below:

$$\underset{\text{(I)}}{\mathrm{Cl(CH_2)_4CCl_3}} \rightarrow \underset{\text{(II)}}{\mathrm{HO(CH_2)_4CCl_3}} \rightarrow$$

$$\underset{\text{(III)}}{\mathrm{HOOC(CH_2)_3CCl_3}} \rightarrow \underset{\text{(IV)}}{\mathrm{HOOC(CH_2)_2CH{=}CCl_2}} \rightarrow$$

$$\underset{\text{(V)}}{\mathrm{HOOC(CH_2)_2CHClCOOH}} \rightarrow$$

$$\underset{\text{(VI)}}{\mathrm{HOOC(CH_2)_2CHNH_2COOH}}$$

Since the trichloromethyl group in I is inert towards a nucleophilic reagent, the chlorine atom at the other end can be substituted selectively by the hydroxy group in an aqueous alkaline solution. In a laboratory, however, the saponification of the acetoxy derivative of I prepared by treating I with potassium acetate in glacial acetic acid is a more convenient method.

According to Nesmeyanov et al.,[3] the oxidation of II by chromic anhydride in glacial acetic acid gave III, but in a poor yield. In our study, II was oxidized with potassium permanganate in an aqueous solution to afford III in a yield over 90%. The trichloroethyl group in aliphatic compounds is converted to dichlorovinyl group by heating in the presence of such a Lewis acid as ferric chloride.[4] The dehydrochlorination of III using such stronger Lewis acids as aluminum chloride and ferric chloride resulted only in a poor yield. However, when III was heated in the presence of a relatively weaker Lewis acid such

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[1] K. Saotome and Y. Kodaira, This Bulletin, **35**, 2010 (1962).

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

[3] A. N. Nesmeyanov, L. I. Zakharkin and R. Kh. Freidlina, *Izv. Akad. Nauk, Otd. Khim. Nauk*, **1955**, 40.

[4] A. N. Nesmeyanov, R. Kh. Freidlina and L. I. Zakharkin, *Quart. Rev.*, **10**, 330 (1956).

as zinc chloride or bismuth chloride, IV was found to be affoded in a good yield. Nesmeyanov et al.³⁾ synthesized IV through another process, in which dichloropropenylmalonic acid prepared from 3, 3, 3-trichloropropene-1 by malonic synthesis was decarboxylated.

The synthesis of α-chlorocarboxylic acid by the chlorination of compounds containing a dichlorovinyl group in an acid medium has been reported recently.⁵⁾ The conjugated addition of chlorine to the dichlorovinyl group is considered to proceed according to the following scheme:

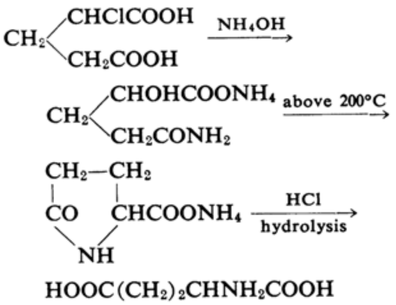
$$RCH{=}CCl_2 \xrightarrow[HA]{Cl_2} [RCHCl\text{-}CCl_2A] \xrightarrow{H_2O}$$

$$RCHClCOOH + 2HCl + HA$$

A chlorine atom and an acid residue (A) are added to the double bond of the dichlorovinyl group, and the resulting adduct is decomposed with water to give α-chlorocarboxylic acid.

Freidlina et al.⁶⁾ synthesized several amino acids by the ammonolysis of α-chlorocarboxylic acids which had been prepared by the above method. In their reports, DL-glutamic acid was also prepared from 5, 5-dichloro-4-pentenoic acid (IV). Since the separation of α-chloroglutaric acid as crystals is somewhat difficult, they obtained the diethyl ester of α-chloroglutaric acid by treating the crude product with ethanol. The ammonolysis of diethyl α-chloroglutarate was carried out with ethanol-ammonia. They obtained DL-glutamic acid in a 70% yield after the hydrolysis of the amination product with hydrochloric acid. Another reason why Freidlina et al. converted the chlorination product to diethyl α-chloroglutarate may be the complicated behavior of α-chloroglutaric acid in ammonolysis.

According to Kawai,⁷⁾ the ammonolysis of α-chloroglutaric acid in aqueous ammonia at a temperature above 200°C proceeds according to the following scheme:



DL-glutamic acid

In our process, α-chloroglutaric acid was separated as crystals from the chlorination product. The ammonolysis of α-chloroglutaric acid was carried out in aqueous ammonia at 260°C, and the resulting product was hydrolyzed with hydrochloric acid to afford DL-glutamic acid in a 87% yield.

Experimental

1, 1, 1-Trichloro-5-hydroxypentane (II).—A mixture of 786 g. of I, 660 g. of potassium acetate and 900 ml. of glacial acetic acid was refluxed for 16 hr. in the presence of the catalyst iodine (1.5 g.). The reaction mixture was diluted with water after the acetic acid had been evaporated under reduced pressure. The oily layer and the benzene extract from the aqueous layer were then combined and washed with water. Distillation of the extract under reduced pressure afforded 1, 1, 1-trichloro-5-acetoxypentane; b. p. 79~80°C/1 mmHg, n_D^{20} 1.4683. Yield, 805 g. (92.0%).

The acetate prepared above was saponified with sodium hydroxide in aqueous methanol (1 : 1) at room temperature. The reaction mixture, after being allowed to stand overnight, was neutralized with hydrochloric acid and extracted with benzene. The distillation of the benzene extract under reduced pressure afforded a quantitative amount of II; b. p. 78~80°C/1 mmHg, n_D^{20} 1.4878 (lit.³⁾ b. p. 112~113°C/10 mmHg, n_D^{20} 1.4897).

5, 5, 5-Trichlorovaleric Acid (III).—Into an aqueous solution of potassium permanganate heated in a water bath, II was stirred in drop by drop. The reaction was continued for a few hours after the

TABLE I. THE OXIDATION OF 1, 1, 1-TRICHLORO-5-HYDROXYPENTANE

$HO(CH_2)_4CCl_3$ g.	$KMnO_4$ g.	H_2O ml.	Temp. °C	Time hr.	$HOOC(CH_2)_3CCl_3$	
					g.	Yield, %
19.1	23.5	140	45~50	(1.0)*+2.0	15.5	75.8
95.5	143	650	50~55	(1.0) +2.0	89.5	87.5
95.5	190	650	55~60	(2.0) +2.0	88.5	85.0
95.5	160	600	55~60	(1.0) +3.0	96.0	93.8
95.5	160	650	55~60	(1.5) +3.0	94.0	92.0

* The value in ( ) represents the time used for the addition of $HO(CH_2)_4CCl_3$.

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5) A. N. Nesmeyanov, R. Kh. Freidlina, V. N. Kost and T. T. Vassilyeva, *Tetrahedron*, **17**, 69 (1962).

6) R. Kh. Freidlina, V. N. Kost and T. T. Vassilyeva, *Izv. Akad. Nauk, Otd. Khim. Nauk*, **1959**, 826.

7) Y. Kawai, *J. Chem. Soc. Japan, Pure Chem. Sec.* (*Nippon Kagaku Zasshi*), **80**, 1321 (1959).

TABLE II. THE DEHYDROCHLORINATION OF 5,5,5-TRICHLOROVALERIC ACID

$HOOC(CH_2)_3CCl_3$ g.	Lewis acid g.	Solvent AcOH, g.	Temp. °C	Time hr.	$HOOC(CH_2)_2CH{=}CCl_2$	
					g.	Yield, %
50.0	$FeCl_3$ 0.5	—	90～100	4.0	21.0	51.0
50.0	$AlCl_3$ 1.0	—	100～110	4.0	26.5	64.5
41.0	$BiCl_3$ 1.5	—	140～150	3.0	28.0	83.2
41.0	$BiCl_3$ 2.0	—	140～150	4.0	28.5	84.6
41.0	$ZnCl_2$ 1.5	—	120～130	4.0	27.0	80.3
41.0	$BiCl_3$ 1.5	12	140～150	4.0	27.5	81.2
41.0	$BiCl_3$ 1.0+0.5*	12	140～150	2.0+2.0	28.5	84.6
41.0	$ZnCl_2$ 1.0+0.5	12	120～130	2.0+2.0	26.5	78.7

* The catalyst was added in two portions 1.0 g. at the beginning of the reaction, and then 0.5 g. after 2 hr.

TABLE III. THE CHLORINATION OF 5,5-DICHLORO-4-PENTENOIC ACID

$HOOC(CH_2)_2CH{=}CCl_2$ g.	Acid g.	Temp. °C	Time hr.	$HOOC(CH_2)_2CHClCOOH$	
				g.	Yield, %
25.0	H_2SO_4 (96%) 31	5～10	3	17.0	69.5
20.0	H_2SO_4 (96%) 32	5～10	5	13.0	68.5
26.0	H_2SO_4 (90%) 65	5～10	5	20.0	78.0
31.0	H_2SO_4 (90%) 90	3～ 8	5	25.0	82.0
32.0	H_2SO_4 (92%) 80	3～ 8	5	22.0	70.0
20.0	HCOOH 60	3～ 8	5	16.0	81.5
26.0	CH_3COOH 80	3～ 8	5	18.0	70.5

addition of the reactant. The excess permanganate was decomposed by adding a small amount of methanol. The manganese dioxide which was precipitated was filtered from the reaction mixture and washed several times with hot water. The filtrate was then cooled and acidified with hydrochloric acid. The white crystals which precipitated were collected and dried over calcium chloride under reduced pressure. Recrystallization from petroleum ether afforded III; m. p. 64°C (lit. m. p. 65°C).

Found: C, 29.19; H, 3.41; Cl, 51.82. Calcd. for $C_5H_7O_2Cl_3$: C, 29.23; H, 3.43; Cl, 51.77%.

Details of the reaction are shown in Table I.

5, 5-Dichloro-4-pentenoic Acid (IV). — The dehydrochlorination of III was investigated using several Lewis acids as catalysts. The reaction was carried out by heating and simultaneously stirring III in the presence of the catalyst. After the evolution of hydrogen chloride had ceased, the reaction mixture was washed with water, then distilled under reduced pressure to afford IV; b. p. 95～97°C/1 mmHg, n_D^{20} 1.4888 (lit.[3] b. p. 93～94°C/1 mmHg, n_D^{20} 1.4898).

Found: C, 35.32; H, 3.68; Cl, 41.83. Calcd. for $C_5H_6O_2Cl_2$: C, 35.53; H, 3.58; Cl, 41.96%.

The reaction conditions and the yields are shown in Table II.

As Table II shows, when a stronger Lewis acid ($AlCl_3$ or $FeCl_3$) was used as the catalyst, the resinous by-product increased and the yield of IV decreased. The best result was obtained when bismuth chloride was used as the catalyst. The effect of acetic acid as a solvent was not prominent.

α-Chloroglutaric Acid (V). — Into sulfuric acid cooled in ice-water, IV was dissolved slowly to make a clear solution. Chlorine gas was passed through this solution while it gas being stirred at a temperature below 10°C. The reaction was continued for a few hours until the evolution of hydrogen chloride had ceased. The reaction mixture was then poured into ice-water, and the product was extracted with ether. The ether extract was washed several times with water and dried with anhydrous sodium sulfate. After the evaporation of the ether, the residue was further dried under reduced pressure to obtain the crystals of V. Recrystallization from chloroform afforded white crystals; m. p. 95～97°C, (lit. m. p. 98°C).

Found: C, 36.19; H, 4.24; Cl, 21.43. Calcd. for $C_5H_7O_4Cl$: C, 36.05; H, 4.24; Cl, 21.29%.

In this reaction, formic and acetic acids were also applied in place of sulfuric acid. The reaction product was then treated as in the case of sulfuric acid. Details of the reaction are shown in Table III.

DL-Glutamic Acid (VI).—In an autoclave equipped with a magnetic stirrer, V (5.0 g.) and aqueous ammonia were placed. The reaction was carried out at the temperature of 260±5°C for 4 hr. The reaction mixture was concentrated almost to dryness on a water bath to remove any free ammonia. The residue was then dissolved in 40 ml. of hot water and filtered.

To this filtrate 40 ml. of concentrated hydrochloric acid was added, and the mixture was refluxed for 4 hr. to hydrolyze the reaction product. The solution was again concentrated to dryness under reduced pressure to remove hydrochloric acid. The solid product was dissolved in 100 ml. of water, and the solution was decolorized by boiling it with active charcoal. The decolorized solution was then concentrated to about 30 ml. An aliquot of this solution was directed to the sample for the quantitative analysis of VI. The pH of the rest of the solution was adjusted at 3.2 (the isoelectric point of glutamic acid) and stored in a refrigerator. White crystals precipitated. Recrystallization from water gave VI; m. p. 185°C (lit. m. p. 185°C). This was identified by paper chromatography with an authentic sample and was shown to be one-spot.

Found: C, 40.67; H, 6.38; N, 9.39. Calcd. for $C_5H_9O_4N$; C, 40.82; H, 6.17; N, 9.52.

The Quantitative Analysis of DL-Glutamic Acid. —Five milliliters of the decolorized solution was diluted to 100 ml., of which 0.01 ml. was taken on a filter paper; the components other than DL-glutamic acid were removed by electrophoresis. The DL-glutamic acid was then extracted with ethanol from the paper, and the resulting solution was analyzed by electrophotometry. The DL-glutamic acid content was determined by comparison with the standard extinction curve. The relation between the concentration of aqueous ammonia and the yield is show in Table IV.

TABLE IV. THE AMMONOLYSIS OF α-CHLOROGLUTARIC ACID

α-Chloroglutaric acid	Aqueous NH_3		DL-Glutamic acid	
g.	ml.	concn., %	g.	Yield, %
5.0	50	13.5	3.84	87
5.0	50	20.0	3.31	75
5.0	50	28.0	3.09	70

In Tabl IV, the yield may be seen to decrease as the concentration of ammonia increases.

Summary

DL-Glutamic acid has been synthesized from 1, 1, 1, 5-tetrachloropentane. The process involves five steps through 1, 1, 1-trichloro-5-hydroxypentane (92%), 5, 5, 5-trichlorovaleric acid (94%), 5, 5-dichloro-4-pentenoic acid (85%), α-chloroglutaric acid (82%), and DL-glutamic acid (87%). The over-all field from 1, 1, 1, 5-tetrachloropentane to DL-glutamic acid was 52%.

In the dehydrochlorination of 5, 5, 5-trichlorovaleric acid to 5, 5-dichloro-4-pentenoic acid, rather weak Lewis acid catalysts, such as bismuth chloride and zinc chloride were found to give the best results.

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