A Novel Synthesis of L-2-Amino-4,4,4-trichlorobutanoic Acid[1]

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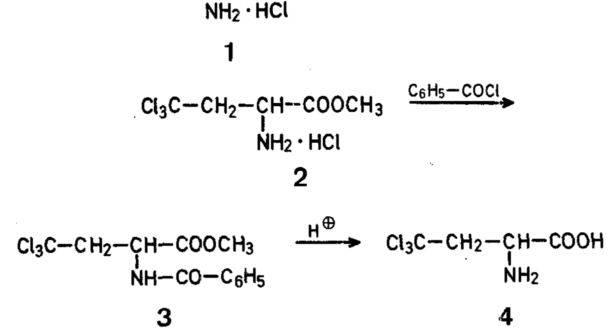
Halogeno-α-amino acids, especially γ,γ,γ-trihalogeno-α-amino acids, have become attractive as antagonists of the naturally occuring α-amino acids. They could be useful to clarify the regulatory mechanisms of the biosynthesis of α-amino acids, and to isolate α-amino-acid analog-resistant mutants. Although several methods[2,3] for the synthesis of DL-γ,γ,γ-trihalogeno-α-amino acids have been reported, the synthesis of optically active ones has not been described.

In the present study, the chlorinolysis of L-methionine methyl ester hydrochloride (1) with molecular chlorine[4] was carried out, resulting in methyl L-2-amino-4,4,4-trichlorobutanoate (2) which was isolated as methyl 2-benzoylamino-4,4,4-trichlorobutanoate (3). Optically active 2-amino-4,4,4-trichlotobutanoic acid (4) was obtained by hydrolysis of 3.



$$H_3C-S-CH_2-CH_2-\underset{NH_2\cdot HCl}{CH}-COOCH_3 \xrightarrow{Cl_2/CHCl_3}$$

1

$$Cl_3C-CH_2-\underset{NH_2\cdot HCl}{CH}-COOCH_3 \xrightarrow{C_6H_5-COCl}$$

2

$$Cl_3C-CH_2-\underset{NH-CO-C_6H_5}{CH}-COOCH_3 \xrightarrow{H^{\oplus}} Cl_3C-CH_2-\underset{NH_2}{CH}-COOH$$

3 4

The reaction sequence represents a useful method to prepare optically active γ,γ,γ-trichloro-α-amino acids without racemization because of the mild conditions employed.

Methyl L-2-Benzoylamino-4,4,4-trichlorobutanoate (3):
A solution of chlorine (10.6 g, 0.15 mol) in chloroform (100 ml) was added portionwise to a stirred slurry of L-methionine methyl ester hydrochloride (1; 5.0 g, 0.025 mol) in dry chloroform (100 ml) at −5 to 0°. Stirring was continued at 10° for 24 h, while a gentle stream of chlorine was bubbled through the mixture. After excess chlorine had been removed by a stream of nitrogen at 10°, the reaction mixture was evaporated under reduced pressure. The residue was dissolved in water (100 ml) and extracted with ether to remove non-amino acids. The aqueous solution containing the amino-acid ester was benzoylated with benzoyl chloride by the usual method. The resultant products were purified by crystallization from ethanol; yield: 2.27 g (28%); m.p. 179–181°; $[\alpha]_D^{22}$: −46.8° (c=1, DMF).

$C_{12}H_{12}Cl_3NO_3$	calc.	C 44.39	H 3.73	Cl 32.77	N 4.32
(324.6)	found	44.69	3.83	32.45	4.27

I.R. (Nujol): ν_{max}=3340, 1737 cm^{-1}.

^{1}H-N.M.R. (DMSO-d_6): δ=8.77 (d, 1H, NH, J=8 Hz), 7.3–8.08 (m, $5H_{arom}$), 5.06 (m, 1H, CH), 3.75 (s, 3H, OCH_3), 3.46 ppm (d, 2H, CH_2, J=5 Hz).

Irradiation of the methine proton at δ=5.06 ppm (60 MHz) caused a collapse of the doublets at δ=3.46 and 8.77 ppm to a singlet.

M.S.: m/e=323 (M^+), and isotope peaks at $M^+ +2$, $M^+ +4$, $M^+ +6$. We ascertained that the M.S. pattern resembles closely that calculated for a trichloro compound.

L-2-Amino-4,4,4-trichlorobutanoic Acid (4):
Methyl L-2-benzoylamino-4,4,4-trichlorobutanoate (10 g, 30.8 mmol) was hydrolyzed with 6N hydrochloric acid (500 ml) at 90° for 12 h. The mixture was evaporated to dryness in vacuo to remove excess hydrochloric acid. The residue was dissolved in water (50 ml) and washed with chloroform. The aqueous solution was adjusted to pH 4.0 by the addition of 10% aqueous ammonia, and the mixture was evaporated in vacuo at 30°. The resultant crystals were recrystallized from water; yield: 3.98 g (62%); m.p. 169° (dec); $[\alpha]_D^{22}$ −9.67° (c=0.84, water).

$C_4H_6Cl_3NO_2$	calc.	C 23.26	H 2.93	Cl 51.5	N 6.78
(206.5)	found	23.66	3.20	50.9	6.86

I.R. (Nujol): ν_{max}=2150–2700 ($\overset{\oplus}{N}H_3$), 1620 cm^{-1} ($COO^{\ominus}$).
^{1}H-N.M.R. (CF_3COOD): δ=4.95 (q, 1H, CH), 3.67 ppm (oct, 2H, CH_2).

The amino acid obtained was homogeneous by paper partition chromatography: R_F 0.98 (butanol/acetic acid/water 4:1:1).

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[1] Formation of Optically Active Amino Acids; 5.
Part 4: T. Iwasaki, M. Miyoshi, M. Matsuoka, K. Matsumoto, *Chem. & Ind.* **1973**, 1163.

[2] H. M. Walborsky, M. E. Baum, *J. Org. Chem.* **21**, 538 (1954).

[3] W. Steglich, H. U. Heininger, H. Dworschak, F. Weygand, *Angew. Chem.* **79**, 822 (1967); *Angew. Chem. Internat. Edit.* **6**, 808 (1967).

[4] For the chlorolysis of organic sulfides with elemental chlorine, see, for example:
E. Kühle, *Synthesis* **1970**, 568; *The Chemistry of the Sulfenic Acids*, Georg Thieme Verlag, Stuttgart, 1973, p. 13.