New Synthesis of Amino Acids from Halogenated Carboxylic Esters[**]

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Dedicated to Professor Hellmut Bredereck on the occasion of his 75th birthday

Synthetic natural and unnatural α-amino acids are gaining increasing importance in medicine and in the fortification of foods and animal feeds[1].

Direct amination of α-halo carboxylic acids with aqueous ammonia in many cases leads to secondary and tertiary amino compounds. This multiple alkylation can be largely suppressed by addition of ammonium salts or by working in liquid ammonia[2]; separation of the various salts, though, from the amino acids also present as salt mixtures, often causes considerable experimental difficulties.—Contrary to earlier reports[3], reaction of 2,6-dihalocapronic acids with ammonia, even in the presence of ammonium salts and urotropin, yields mainly 2-piperidinecarboxylic acid, and no lysine.

We have now found that halogenated carboxylic esters *(1)* give high yields of amino acids *(4)* on treatment with alkali cyanates in the presence of alcohols (Table 1). As in the Gabriel synthesis, the amino function is introduced in a protected form [isocyanato or alkoxycarbonylamino group in *(2)* and *(3)*, respectively], yet in a simpler and less expensive way, and the protecting group can be cleaved off under milder conditions. Scattered reports of the reaction between alkali cyanates and alkyl halides in the presence of alcohols, giving urethanes, have already been published[4]. Nothing was known, though, about reactions with derivatives of halo-

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genated carboxylic acids, or about the scope of this method for the preparation of primary amines.

The isocyanato esters *(2)* formed initially from the monohalo compounds *(1)* can be isolated and hydrolyzed to the amino acids; the cyanate-catalyzed oligomerization which is the predominant reaction of 2,6-diisocyanatohexanoic esters under standard conditions can be largely suppressed by addition of alcohol. The urethanes *(3)* can be readily isolated and purified, and are hydrolyzed almost quantitatively to analytically pure amino acid hydrochlorides, *(4)* · HCl (Table 1).

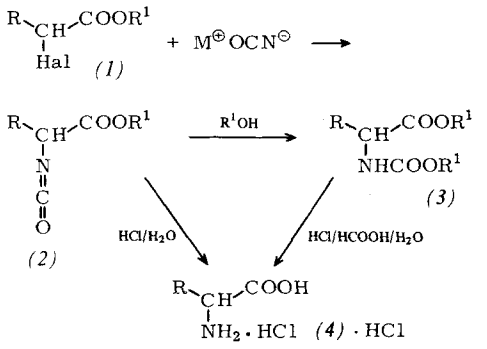


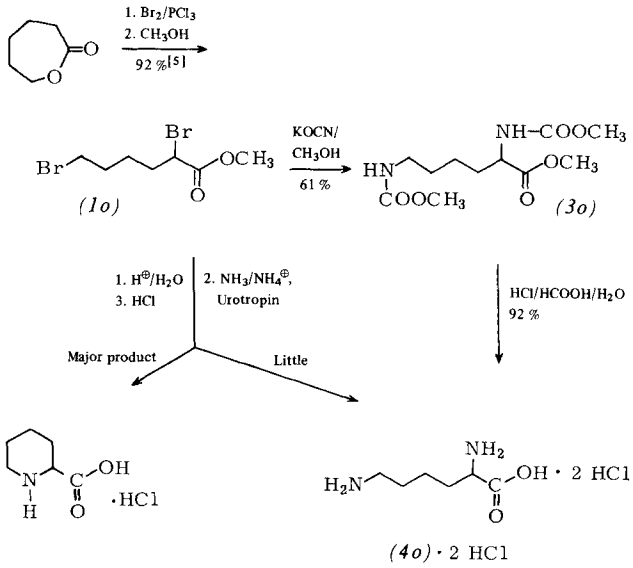
Table 1. Amino acids *(4)* from halo carboxylic esters *(1)*, X = halogen, *via* urethanes *(3)*, X = NHCOOCH₃ (see experimental section).

	Molecular skeleton A = $COOCH_3$	*(1)* X	*(3)* Yield [%]	*(4)*	*(4)* · HCl Yield [%]
a	XCH_2 A	Br	64	Glycine	98
b	CH_3 CHX A	Br	59	Alanine	92
c	$C_6H_5CH_2$ CHX A	Br	2.4	Phenylalanine	97
d	C_2H_5 CHX A [a]	Br	55	2-Amino-butyric acid	92
e	X $(CH_2)_3$ A	Br	67	4-Amino-butyric acid	97
f	$(CH_3)_2CH$ CHX A	Br	21	Valine	99
g	X $(CH_2)_4$ A	Br	65	5-Aminovaleric acid	96
h	n-C_4H_9 CHX A	Br	76	Norleucine	97
i		Cl	67		
j	[a]	Br	63	Norleucine	94
k	i-C_4H_9 CHX A	Br	66	Leucine	91
l	X $(CH_2)_5$ A	Cl	70	6-Amino-hexanoic acid	94
m	Cl $(CH_2)_4$ CHX A	Br	61	2-Amino-6-chloro-hexanoic acid	90
n	X $(CH_2)_2$ CHX A	Br	47	2,4-Diamino-butyric acid	98 [b]
o	X $(CH_2)_4$ CHX A	Br	61	Lysine	92 [b]

[a] $COOC_2H_5$ in place of $COOCH_3$ in *(1)* and *(3)*; $NHCOOC_2H_5$ in place of $NHCOOCH_3$ in *(3)*. [b] *(4)* · 2HCl.

The predominant formation of isocyanates *(2)* as well as the influence of the solvent and of the nature of the cation all suggest a S_N2 mechanism for this reaction. This assumption also rationalizes the observation that additional alkyl groups at the substitution center or increasing steric hindrance at the adjacent carbon atom reduce or even preclude substitution in favor of elimination, as in the case of methyl α-bromoisobutyrate. Preferred elimination thus disqualifies the method for the amination of β-halo- and β-phenyl-α-halo carboxylic esters [see, *e.g.*, *(1c)*].

Synthesis of DL-lysine from ε-caprolactone in an overall yield of 52% is an important application of the new amination procedure.



Experimental

Halo carboxylic ester *(1)* (10 mmol) in anhydrous dimethylformamide (DMF) is heated to 100 °C with stirring with finely ground and dried potassium cyanate and alcohol R^1OH (15 mmol and 35 mmol, respectively, per halogen atom to be replaced; 40—60 min for bromine compounds, 30 h for chlorine compounds). After filtration and removal of DMF by distillation, acetone (30 ml) is added to quantitatively separate the salts. The monourethanes are fractionated in a high vacuum, and the diurethanes are purified by liquid chromatography[6]. The pure urethanes *(3)* are hydrolyzed by refluxing with a mixture of equal parts of conc. hydrochloric acid, 100% formic acid, and water for 20 h at 125 °C. After removal of the mixture of acids, the residue is washed several times with acetone, and the crystalline amino acid hydrochlorides are filtered off and dried in a high vacuum.

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(1a), 96-32-2; *(1b)*, 57885-43-5; *(1c)*, 70288-60-7; *(1d)*, 66025-42-1; *(1e)*, 4897-84-1; *(1f)*, 70332-52-4; *(1g)*, 5454-83-1; *(1h)*, 70288-61-8; *(1i)*, 70288-62-9; *(1j)*, 63927-44-6; *(1k)*, 70288-63-0; *(1l)*, 14273-89-3; *(1m)*, 70288-64-1; *(1n)*, 70288-65-2; *(1o)*, 70288-66-3; *(2a)*, 30988-17-1; *(2b)*, 30293-83-5; *(2c)*, 30293-84-6; *(2d)*, 70288-67-4; *(2e)*, 27678-30-4; *(2f)*, 30293-87-9; *(2g)*, 70288-68-5; *(2h)*, 70288-69-6; *(2j)*, 70288-70-9; *(2k)*, 30293-88-0; *(2l)*, 29640-13-9; *(2m)*, 70288-71-0; *(2n)*, 70288-72-1; *(2o)*, 70332-53-5; *(3a)*, 70288-73-2; *(3b)*, 70288-74-3; *(3c)*, 70288-75-4; *(3d)*, 70288-76-5; *(3e)*, 70288-77-6; *(3f)*, 70304-35-7; *(3g)*, 70320-18-2; *(3h)*, 70288-78-7; *(3g)*, 70288-79-8; *(3k)*, 70304-20-0; *(3l)*, 70288-80-1; *(3m)*, 70288-81-2; *(3n)*, 70288-82-3; *(3o)*, 70288-83-4; *(4a)*, 6000-43-7; *(4b)*, 25616-13-1; *(4c)*, 27172-85-6; *(4d)*, 40522-79-0; *(4e)*, 5959-35-3; *(4f)*, 25616-14-2; *(4g)*, 627-95-2; *(4h)*, 70288-84-5; *(4k)*, 2508-63-6; *(4l)*, 4321-58-8; *(4m)*, 70288-85-6; *(4n)*, 65427-54-5; *(4o)*, 617-68-5;

[1] See, *e.g.*, *Y. Izumi, J. Chibata, T. Itoh*, Angew. Chem. 90, 187 (1978); Angew. Chem. Int. Ed. Engl. 17, 176 (1978).
[2] *N. D. Cheronis, K. H. Spitzmueller*, J. Org. Chem. 6, 349 (1941); H. H. Sisler, N. D. Cheronis, *ibid.* 6, 467 (1941).
[3] *D. C. Sayles, E. F. Degering*, J. Am. Chem. Soc. 71, 3161 (1949); *K. H. König, H. Pommer*, DAS 1296642 (1969), BASF.
[4] *D. W. Kaiser*, US-Pat. 2647916 (1953) and 2697720 (1954), American Cyan-

  0570-0833/79/0606-0475 $ 02.50/0

mid; Chem. Abstr. *48*, 1433g (1954) and *49*, 8331i (1955); *P. A. Argabright, H. D. Rider, R. Sieck*, Org. Chem. *30*, 3317 (1965); *W. Gerhardt*, Tenside *2*, 101 (1965).
[5] *F. Effenberger, G. Clar, H. Haschke, W. Leuchtenberger, G. Schreyer, W. Schwarze*, DOS 2440212 (1976), DEGUSSA.
[6] *B. Glatz, G. Helmchen*, to be published.

