A New Method for the Preparation of Hydrochlorides (hydrobromides) of Amino Acids

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Hydrochlorides of amino acids are generally prepared by evaporating their solution in hydrochloric acid. This, however, does not always lead to the pure salts.

We have now worked out a new simple method by means of which hydrochlorides may be prepared, with a few exceptions, in very high yield and great purity without further recrystallization. The method is based on the observation that N,N^2-dibenzylasparagine hydrochloride is precipitated on dissolving the amino acid in a mixture of acetyl chloride—glacial acetic acid.[1] The hydrochlorides are prepared according to one of the following three procedures:

TABLE I

Preparation of Hydrochlorides (Hydrobromides)

Substance, Amino Acid HCl (HBr)	Method[a]	Yield, %	M.p., ° C.	Formula	Nitrogen		Halogen	
					Calc'd	Found	Calc'd	Found
Glycine-HCl	B	96	186	$C_2H_6ClNO_2$	12.6	12.5	31.7	31.5
DL-Alanine-HCl	C	98	156	$C_3H_8ClNO_2$	11.2	11.2	28.3	28.0
β-Alanine-HCl	A	97	122	$C_3H_8ClNO_2$	11.2	10.9	28.3	28.3
DL-Acetylserine-HCl	A	91	152	$C_5H_{10}ClNO_4$	7.6	7.7	19.4	19.6
L-Cysteine-2HCl	B	94	220	$C_6H_{14}Cl_2N_2O_4S_2$	8.9	8.8	22.7	21.8
Methionine-HCl	A	41	145	$C_5H_{12}ClNO_2S$	7.5	7.3	19.1	19.1
DL-Valine-HCl	A	99	189	$C_5H_{12}ClNO_2$	9.1	8.9	23.0	22.8
L-Leucine-HCl	A	83	190	$C_6H_{14}ClNO_2$	8.4	8.2	21.2	21.3
DL-α-Amino-*n*-butyric acid-HCl	A	93	242	$C_4H_{10}ClNO_2$	10.0	9.8	25.4	25.4
DL-Aspartic acid-HCl	B	20	164	$C_4H_8ClNO_4$	8.2	8.0	20.9	20.8
L-Glutamic acid-HCl	B	61	201	$C_5H_{10}ClNO_4$	7.6	7.4	19.4	19.6
DL-Phenylalanine-HCl	A	99	215	$C_9H_{12}ClNO_2$	7.0	6.8	17.5	17.5
L-Tyrosine-HCl	A	99	215	$C_9H_{12}ClNO_3$	6.3	6.0	16.5	16.4
DL-Tryptophane-HCl	A	39	194	$C_{11}H_{13}ClN_2O_2$	11.6	10.7	14.7	14.6
Glycine-HBr		83	247	$C_2H_6BrNO_2$	9.0	8.9	51.3	51.0
DL-Alanine-HBr		79	140	$C_3H_8BrNO_2$	8.2	8.0	47.1	47.3
DL-α-Amino-*n*-butyric acid-HBr		46	125	$C_4H_{10}BrNO_2$	7.6	7.2	43.4	43.2
L-Leucine-HBr		47	197	$C_6H_{14}BrNO_2$	6.6	6.4	37.7	37.9
DL-Phenylalanine-Hbr		75	204	$C_9H_{12}BrNO_2$	5.7	5.4	32.5	33.2
L-Tyrosine-HBr		98	245	$C_9H_{12}BrNO_3$	5.3	4.6	30.5	31.3

[a] The most suitable method for each amino acid is indicated.

(*A*). To one gram of the finely pulverized amino acid is added 15 ml. of glacial acetic acid and 15 ml. of acetyl chloride. The reaction mixture is shaken at room temperature for 20 minutes, during which time the constitution of the originally suspended substance changes markedly. Finally 250 ml. of dry ether is added which causes complete precipitation of the partly dissolved hydrochloride. In a few cases, the substance at first has an oily constitution. However, on decanting the ether, adding fresh solvent and leaving overnight in an ice box, crystals are obtained. The substances are mostly sufficiently pure, but they may be recrystallized by dissolving in absolute ethanol and precipitating with dry ether.

Serine suffers acetylation and O-acetylserine hydrochloride results. Thus the more complicated O-acetylation procedure of Sakami and Toenis[2] may be avoided.

(*B*). One gram of the amino acid is dissolved in the smallest possible quantity of concentrated hydrochloric acid and to the cooled solution 15 to 20 ml. of acetyl chloride is added (5 ml. of acetyl chloride for each ml. of concentrated hydrochloric acid). On addition of 200 ml. of dry ether, the hydrochloride is precipitated.

(*C*). Dry hydrochloric acid is introduced into cooled glacial acetic acid for one hour. One gram of the amino acid is shaken with 20 ml. of this solution for 20 minutes and finally 250 ml. of dry ether is added.

Hydrobromides are prepared as follows: To one gram of the amino acid is added 10 ml. of a mixture of concentrated hydrobromic acid and acetic anhydride (1:1). The reaction mixture is shaken for 20 minutes and then 20 ml. of acetic anhydride,[3] and after cooling, 250 ml. of dry ether is added and as soon as precipitation sets in, 200 ml. of a mixture of ether-petroleum ether (1:1). If the product is oily, it is left in an ice box overnight.

Finally, it may be remarked, that these salts were advantageously used for the characterisation of the parent amino acids, since they are easily obtained in a crystalline state with definite and different melting points.

Preparations are listed in Table I.

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(1) Y. Liwschitz, A. Zilkha, and Y. Amiel, *J. Am. Chem. Soc.*, **78**, 3067 (1956).

(2) W. Sakami and G. Toenis, *J. Biol. Chem.*, **144**, 203 (1942); Max Frankel, S. Cordova, and M. Breuer. *J. Chem. Soc.*, 1991 (1953).

(3) This is added solely for the purpose of obtaining a crystalline, easily filterable product.