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The Convenient Preparation of L-Aspartic Anhydride Hydrochloride and Hydrobromide

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L-Aspartic anhydride hydrochloride (I) and hydrobromide (II) are useful intermediates for the preparation of aspartyl peptides,[1] aspartic acid α-esters,[1] and polyaspartic acid.[2] II has been prepared thus far by the deprotection of carbobenzoxy-L-aspartic anhydride with hydrogen bromide in acetic acid[1] or by the direct dehydration of L-aspartic acid with an excess of thionyl chloride in chlorosulfonic acid or trifluoroacetic acid, followed by the removal of the strong acid used as the solvent and treatment with hydrogen bromide in acetic anhydride.[3] The strongly acidic solvent has played a role in protecting the amino group from undesirable reactions during the dehydration reaction. However, it seems that these methods are somewhat inconvenient because of the need to protect the amino group or the use of the strongly acidic solvent. Furthermore, the properties of I have not been reported in the literature.

We wish to report a more convenient method for preparing I and II. The synthesis was conducted as a heterogeneous reaction in a more convenient solvent, tetrahydrofuran, in which the dehydrating reagent is dissolved. The reaction proceeds smoothly according to the equation (Fig. 1). L-Aspartic acid was readily

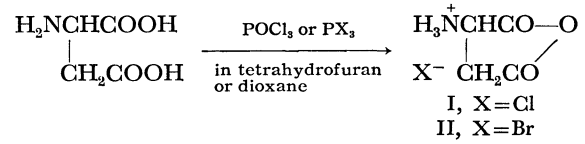

Fig. 1. L-Aspartic anhydride hydrochloride (I) and hydrobromide (II)

dehydrated with phosphorous oxychloride or phosphorous trichloride in tetrahydrofuran at room temperature to give, after filtration, an analytically pure I in a fairly good yield (Table 1). Because of the salt formation at the amino nitrogen, the further condensation of the product to polyaspartic acid does not occur under these conditions. In order to confirm its optical purity, the I obtained here was converted to L-aspartic acid and its optical rotation was measured. The value of the optical rotation of an aqueous solution

Table 1. Summarized data of reactions

No	1	2	3	4
L-Aspartic acid g	13.3	20	13.3	4
Reagent g	$POCl_3$ 15.3	PCl_3 11	$POCl_3$ 15.3	PBr_3 4
Solvent ml	Tetrahydrofuran 200	Tetrahydrofuran 100	Dioxane 150	Tetrahydrofuran 20
Reaction temp °C	25—5	25	25	5
Reaction period hr	5.5	4	6	3.5
Product	I	I	I	II
Yield g (%)	8.0 (53)	21.9 (96)	10.6 (70)	3.2 (54)
Mp °C (decomp.)	139—140	139—140	128—130	157—158[a]
$[\alpha]_D^{25}$	+23.2[b]	+23.3[b]	+24.0[c]	+26.9[d]
IR cm^{-1}	1875, 1815, 1790	1875, 1815, 1790	1885, 1795	1875, 1805, 1785
Anal. Found %	C, 31.41; H, 4.21; N, 9.07; Cl, 23.22[e]	C, 31.70; H, 4.27; N, 9.25; Cl, 23.10[e]	C, 36.26; H, 5.44; N, 7.19; Cl, 18.27[f]	C, 24.22; H, 3.27; N, 6.98; Br, 40.98[g]

a) mp 166—169°C (decomp.).[1]
Specific rotations of L-aspartic acid in various solutions (b—d);
b) $[\alpha]_D^{25}$ +24.5° (*c* 2, 6N HCl).
c) $[\alpha]_D^{25}$ +25.0° (*c* 2, 6N HCl with 0.5 molecular equivalent of dioxane).
d) $[\alpha]_D^{25}$ +25.1° (*c* 2, 6N HBr).
e) Calcd for $C_4H_6O_3NCl$: C, 31.70; 3.99; N, 9.24; Cl, 23.40%.
f) Calcd for $C_4H_6O_3NCl \cdot 1/2C_4H_8O_2$: C, 36.84; H, 5.15; N, 7.16; Cl, 18.13%. NMR (D_2O, DSS) of the product: δ 3.80 ppm (4H, singlet, dioxane).
g) Calcd for $C_4H_6O_3NBr$: C, 24.51; H, 3.09; N, 7.15; Br, 40.77%.

1) J. Kovacs, H. N. Kovacs, and R. Ballina, *J. Amer. Chem. Soc.*, **85**, 1839 (1963).
2) J. Kovacs, H. N. Kovacs, I. Könyves, J. Császár, T. Vajda, and H. Mix, *J. Org. Chem.*, **26**, 1084 (1961).
3) J. Kollonitsch and A. Rosegay, *Chem. Ind.*, **1964**, 1867; *Chem. Abstr.*, **64**, 9820f (1966).

of hydrochloric acid in which a given amount of I had been dissolved agreed with that of an aqueous solution of hydrochloric acid containing the corresponding amount of L-aspartic acid (Table 1). These results show that no racemization occurred during the dehydration reaction. Attempts to measure the optical rotation of the anhydride itself in *N,N*-dimethylformamide, dimethyl sulfoxide, or pyridine did not give reproducible results. The anhydride hydrochloride decomposed slightly in such a solvent, even under anhydrous conditions.

When dioxane was used as the solvent for the dehydration reaction, the anhydride (I) contained half a mole of dioxane as the solvent of crystallization; this was confirmed by the elemental analysis and by the NMR spectrum of I (Fig. 1 and Table 1).

A similar treatment of L-aspartic acid with phosphorous tribromide in tetrahydrofuran gave pure L-aspartic anhydride hydrobromide (II) (Fig. 1 and Table 1). The anhydrides (I and II) decomposed slowly on exposure to atmospheric moisture, but they were found to be stable for more than two weeks when stored *in vacuo* over phosphorous pentoxide. Their use for peptide synthesis will be described elsewhere.

Experimental

All the melting points are uncorrected. The IR spectra were obtained in Nujol mull with a Jasco IR-S spectrometer. The optical rotations were measured in 6N hydrochloric acid or 6N hydrobromic acid with a visual polarimeter.

L-Aspartic Anhydride Hydrochloride (I). A typical run (No. 1 in Table 1) was as follows. To a stirred suspension of L-aspartic acid (13.3 g) in tetrahydrofuran (200 m*l*) was added phosphorous oxychloride (15.3 g) at 25°C over a period of 5 min. The mixture was stirred for 1.5 hr at the same temperature. After being stirred for an additional 4 hr at 5—10°C, the crystals thus formed were collected by filtration and washed with tetrahydrofuran. The anhydride hydrochloride so obtained was analytically pure without further purification. Purification by recrystallization is ineffective because the anhydride slightly decomposes in a solution, as has been described in connection with the attempted measurements of its optical rotation.

In the case of phosphorous trichloride (No. 2 in Table 1), the crystals obtained were accompanied with a disagreeable odor but the odor could be removed by adding acetic acid (20 m*l*) to the reaction mixture before filtration.

The results are summarized in Table 1.

L-Aspartic Anhydride Hydrobromide (II). This compound was prepared by the direct dehydration of L-aspartic acid with phosphorous tribromide in tetrahydrofuran according to the procedure described in connection with the preparation of I. The results are shown in Table 1.

As moisture may cause the anhydrides (I and II) to undergo decomposition, dried solvents should be empolyed in order to obtain satisfactory results in their preparation.