The Methyl Esterification of Amino Acids with 2,2-Dimethoxypropane and Aqueous Hydrogen Chloride[1]

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The hydrochlorides of the esters of amino acids have been prepared usually by treatment of a suspension of the respective amino acid in the required anhydrous alcohol with gaseous hydrogen chloride or with thionyl chloride.[2] Concentration of the mixtures resulting from the hydrogen chloride method with some amino acids (*e.g.*, methionine) often gives sirups which can be crystallized only with difficulty. Retention in the residue of the water produced during the esterification reaction is probably largely responsible for these manipulative problems.

We wish to present here a method for the preparation of the methyl ester hydrochlorides of the amino acids in which 2,2-dimethoxypropane (the methyl ketal of acetone) serves as a source of the methoxyl group, as the major solvent in the reaction system, and as a reactive reagent for the removal of water by virtue of hydrolysis of the ketal to methanol and acetone. The procedure appears to be generally applicable to the amino acids, does not require the use of gaseous hydrogen chloride or of especially dried solvents, and lends itself well to small scale operation.

Experimental

General Procedure.—The methyl ester hydrochlorides of several different types of amino acids, listed in Table I, were obtained in the following manner. One millimole of the amino acid (the hydrochloride in the case of L-lysine) was suspended in 10–15 ml. of 2,2-dimethoxypropane (b.p.[3] 79–81°) and to the suspension was added 1 ml. of 36% aqueous hydrochloric acid. The mixture was allowed to stand at room temperature for 18 hr. In the case of L-lysine and of L-glutamic acid, because of their insolubility, the mixtures were supplemented with 3–4 ml. of methanol, heated to reflux for 2 and 5 hr., respectively, and then allowed to stand for 18 hr. at room temperature. All mixtures darkened considerably on standing, more so after reflux. The mixtures were concentrated by vacuum at 50–60° and the residues were dissolved in a minimum amount of absolute methanol. Addition of about 25 ml. of absolute ethyl ether resulted in crystallization of the desired products. The compounds were recrystallized from methanol–ether. The specific rotations of the optically active compounds are given in Table II.

TABLE I

Methyl ester hydrochloride of	M.p.,[c] °C.	Yield,[d] %	Analysis, % N Found	Calcd.
glycine	174–175	81	11.22	11.15
L-methionine	147–150	95	6.96	7.02
L-leucine	146–148	86	7.72	7.71
L-tyrosine	189–190	90	6.06	6.05
L-lysine[a]	203–205	82	11.95	12.01
L-glutamic acid[b]	88–90	94	6.68	6.61

[a] The dihydrochloride. [b] The diester. [c] Melting points are corrected capillary melting points except for the lysine and glutamic acid derivatives, which were micro melting points (corrected). [d] The yields are for the final analytical samples.

TABLE II

SPECIFIC ROTATION DATA FOR THE METHYL ESTER HYDROCHLORIDES

Derived from	*c*, solvent	Temp., °C.	$[\alpha]_D$ Found	$[\alpha]_D$ Literature[c]
L-methionine	5.1, water	19.5	+25.2°	+26.8°
L-leucine	4.9, water	20.0	+13.2°	−13.4°[d]
L-tyrosine	3.0, pyridine	20.0	+78.1°	+74.3°
L-lysine[a]	5.0, water	20.5	+17.0°	*e*
L-glutamic acid[b]	5.0, water	21.0	+26.0°	*e*

[a] The dihydrochloride. [b] The diester. [c] See ref. 2. [d] The specific rotation of L-leucine methyl ester hydrochloride is erroneously given with a negative sign in ref. 2, and in the original paper of H. F. Schott, J. B. Larkin, L. B. Rockland, and M. S. Dunn, *J. Org. Chem.*, 12, 490 (1947). Our starting leucine had the same specific rotation as that used by Schott, *et al.* The $[\alpha]^{20}D$ of a commercial sample of L-leucine methyl ester hydrochloride (Mann Research Laboratories, grade M.A., lot no. C1107) was found to be +12.3° (*c* 5, water). [e] Not previously published.

The usefulness of 2,2-dimethoxypropane as a solvent and reagent was demonstrated in another respect. The product obtained as described earlier with L-lysine gave a nitrogen analysis (10.55%) which fitted exactly for the methyl ester dihydrochloride of lysine in combination with one molecule of methanol. Observation of the melting of this compound under the microscope showed that there occurred, in sequence, liquefaction between 60–75°, resolidification into another crystalline form, and final melting at 199–200°. Subjecting the compound to high vacuum drying did not result in any loss of weight. The lysine derivative (200 mg.) was then recrystallized from 0.5 ml. of water by the addition of 3 ml. of acetone and 8 ml. of 2,2-dimethoxypropane. The expected methyl ester dihydrochloride of L-lysine crystallized from the mixture as the water was removed by reaction with the ketal.

The application of the preceding procedure with the ketal of acetone and the appropriate alcohol should result in the formation of the corresponding ester hydrochlorides of the amino acids.

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(2) J. P. Greenstein and M. Winitz, "Chemistry of the Amino Acids," John Wiley and Sons, Inc., New York, N. Y., 1961.

(3) Redistilled from the commercial product obtained from Calbiochem, Los Angeles, Calif.

α-Aminophosphinic Acids and α-Aminophosphine Oxides. I. Alkyl-α-aminoalkylphosphinic Acids, α-Aminoalkyl(aryl)phosphinic Acids, and α-Aminoalkyl(diaryl)phosphine Oxides

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The well known Michaelis–Arbuzov reaction[1] was chosen as the key reaction in the syntheses. Intermediates and products are shown in formulas I–XIV and XV–XVIII, respectively. Details of their preparation, purification, and identification are given in the Experimental section. With one exception, *i.e.*, the reaction of IV with II, the Michaelis–Arbuzov reaction products were isolated, purified, and identified. During

(1) G. M. Kosolapoff, "Organophosphorus Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 121.