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.

Acknowledgment.—The author wishes to thank Mr. Joseph Albert for the nitrogen analyses of the compounds presented in this note.

(1) This investigation was supported by a grant (no. CA-03981-06) from the National Cancer Institute of the U. S. Public Health Service.

(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.

TABLE I

MICHAELIS–ARBUZOV REACTIONS

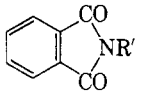
Product	Reactants	Solvent	Temp., °C.	Pressure	Recovery	Recrystn.	Yield, %	M.p., °C.
VII	I, III	Xylene	Reflux	Atm.	Filtered ppt.	Dioxane	89	206–207
VIII	I, IV	Toluene	Reflux	Atm.	Pptd. with *n*-hexane	Benzene–toluene	94	94–96
IX	I, V	Xylene	Reflux	300 mm.	Pptd. at 5°	Benzene–*n*-hexane	86	111–113
X	I, IV	None	120–150	Atm.	Dissolved in benzene; pptd. with diethyl ether	Benzene–*n*-hexane		168–169
XII	I, VI	Xylene	70–80	300 mm.	Pptd. at 10°	Benzene–*n*-hexane	92	109–111
XIV	II, IV	None	115	Atm.	Not isolated			

TABLE II

PHOSPHINIC ACIDS AND PHOSPHINE OXIDE

Product	From	HBr acceptor	Solvent	Temp.	Recovery	Recrystn.	M.p., °C.
XI	VIII	...	...	...	.....	Methanol	270–273
XIII	XII	...	...	...	.....	Ethanol	231–233
XV	VII	Na_2CO_3	Water	Room	To dryness, Soxhlet extraction, hexane	...	102–103[a]
XVI	VIII, IX, X, or XI	Aniline	Ethanol	Reflux	Filter ppt.	75% Ethanol	286–287
XVII	XII	Aniline	Ethanol	Reflux	Filter ppt.	66% Ethanol	296–298
XVIII	[XIV]	Aniline	Acetone	Reflux	Filter ppt.	95% Ethanol	265

[a] Purified by sublimation at *ca.* 100° (0.05 mm.).



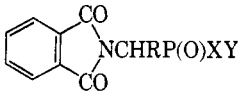
I, R′ = CH_2Br
II, R′ = $CHClCH_3$

—PXYZ—

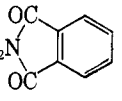
III, X = C_6H_5; Y = C_6H_5; Z = OCH_3
IV, X = C_6H_5; Y = OCH_3; Z = OCH_3
V, X = C_6H_5; Y = OC_2H_5; Z = OC_2H_5
VI, X = CH_3; Y = OC_2H_5; Z = OC_2H_5

—$H_2NCHRP(O)XY$—

XV, R = H; X = C_6H_5; Y = C_6H_5
XVI, R = H; X = C_6H_5; Y = OH
XVII, R = H; X = CH_3; Y = OH
XVIII, R = CH_3; X = C_6H_5; Y = OH



VII, R = H; X = C_6H_5; Y = C_6H_5
VIII, R = H; X = C_6H_5; Y = OCH_3
IX, R = H; X = C_6H_5; Y = OC_2H_5

X, R = H; X = C_6H_5; Y = 

XI, R = H; X = C_6H_5; Y = OH
XII, R = H; X = CH_3; Y = OC_2H_5
XIII, R = H; X = CH_3; Y = OH
XIV, R = CH_3; X = C_6H_5; Y = OC_2H_5

the hydrolysis of VIII and XII it was noted that the ester group was selectively hydrolyzed first and consequently that it was possible to isolate XI and XIII in excellent yield. Under some conditions I and IV give X rather than VIII.

The preparation of XVIII *via* the Michaelis–Arbuzov reaction presented some difficulties. Apparently II (m.p. 110–111°) dehydrochlorinated at the temperature at which methyl chloride began to form (110–115°), and most of IV reacted with the hydrogen chloride liberated rather than with II. The expected intermediate XIV could not be isolated, and hydrolysis of the reaction mixture led to XVIII in only 5% yield based on II. The substitution of V for IV in this reaction was even less satisfactory, for no XVIII at all was recovered.

Experimental

Reactants.—Unless otherwise specified reagent-grade chemicals were used. N-Bromomethylphthalimide (I)[2] and N-(1-chloroethyl)phthalimide (II)[3] were freshly purified before each use to remove any contamination with hydrogen bromide or hydrogen chloride, respectively, which might cause rearrangement of the trivalent phosphorus reactants. Known procedures were employed for the preparation of methyl diphenylphosphinite (III),[4] dimethyl phenylphosphonite (IV),[5] diethyl phenylphosphonite (V),[6] and diethyl methylphosphonite (VI).[7] These trivalent phosphorus compounds were all carefully distilled before each use to eliminate any contamination due to air oxidation or rearrangement.

Michaelis–Arbuzov Reactions.—These condensations were run in a flask equipped with a stirrer, thermometer, nitrogen-inlet tube, addition funnel, and reflux condenser. The outlet of the condenser was connected to a series of two traps cooled with Dry Ice to condense the by-product alkyl halide. The equimolar mixture of the reaction components (with or without solvent) was continuously stirred under a slow stream of nitrogen while the temperature was raised. The reaction temperature was usually 5–20° higher than the temperature at which the alkyl halide began to form. Since it is necessary to remove the alkyl halide speedily in order to avoid its reaction with unchanged phosphonite, reduced pressure was used when ethyl bromide was produced. Heating was discontinued about 20–30 min. after alkyl halide formation stopped. The products were recovered as indicated in Table I and purified by recrystallization. Salient details of the individual reactions are summarized in Table I, elemental analyses are reported in Table III, and infrared characterizations in Table IV.

Conversion of Michaelis–Arbuzov Products.—Reaction products containing the phthalimido group or an ester group were completely hydrolyzed by 5–10 hr. refluxing with an excess of

(2) J. W. Pucher and T. B. Johnson, *J. Am. Chem. Soc.*, **44**, 817 (1922).
(3) K. Kato, *Kogyo Kagaku Zasshi*, **59**, 1006 (1956); *cf. Chem. Abstr.*, **52**, 10002 a (1958).
(4) A. E. Arbuzov and K. V. Nikonorov, *Zh. Obshch. Khim.*, **18**, 2008 (1948).
(5) A. E. Aruzov, *ibid.*, **4**, 898 (1934).
(6) G. Kamai, *ibid.*, **18**, 443 (1948).
(7) F. W. Hoffmann and T. R. Moore, *J. Am. Chem. Soc.*, **80**, 1150 (1958).

TABLE III
ANALYTICAL RESULTS

Compound	Calcd. C	Calcd. H	Calcd. N	Calcd. P	Found C	Found H	Found N	Found P
VII, $C_{21}H_{16}NO_3P$	69.80	4.43	3.88	8.60	69.31	4.18	3.85	8.64
VIII, $C_{16}H_{14}NO_4P$	61.10	4.48	4.45	9.84	61.25	3.94	4.45	9.88
IX, $C_{17}H_{16}NO_4P$	61.99	4.33	4.48	9.54	62.00	4.86	4.25	9.43
X, $C_{24}H_{17}N_2O_6P$	62.70	3.74	6.10	6.73	62.67	4.00	5.97	7.13
XI, $C_{15}H_{12}NO_4P$	59.90	4.03	4.66	10.29	59.74	3.97	4.75	10.87
XII, $C_{12}H_{14}NO_4P$	53.93	5.28	5.24	11.59	53.40	4.78	5.05	11.20
XIII, $C_{10}H_{10}NO_4P$	50.22	4.21	5.86	12.95	49.90	4.44	6.44	12.40
XV, $C_{13}H_{14}NOP$	67.50	6.15	6.06	13.38	67.54	6.23	5.40	13.38
XVI, $C_7H_{10}NO_2P$	49.06	5.85	8.18	18.10	49.10	5.83	8.30	17.70
XVII, $C_2H_8NO_2P$	22.02	7.39	12.84	28.41	22.00	6.80	12.71	28.28
XVIII, $C_8H_{12}NO_2P$	51.89	6.54	7.76	16.73	51.35	6.25	7.75	16.24

TABLE IV
INFRARED ABSORPTIONS (CM.$^{-1}$) AND ASSIGNMENTS

Compound	
XII	1035 (P–O–C), 1215 (P ⟶ O), 1712 [C(O)N]
XIII	1244 (P ⟶ O), 1715 [C(O)N], 2632 (P–OH)
XV	996 (P–C_6H_5), 1186 (P ⟶ O), 1439 (P–C_6H_5), 3268 and 3322 (NH_2)
XVI	998 (P–C_6H_5), 1130 and 1170 (P ⟶ O), 1439 (P–C_6H_5), 2353 to 2500 (zwitterion character), 2597 (P–OH), 3125 to 3333 (H-bonding)
XVII	1136 and 1156 (P ⟶ O), 2353 to 2500 (zwitterion character), 2597 (P–OH)
XVIII	996 (P–C_6H_5), 1131 and 1156 (P ⟶ O), 1439 (P–C_6H_5), 2353 to 2500 (zwitterion character), 2597 (P–OH)

48% aqueous hydrobromic acid. The phthalic acid formed was filtered off at 5–20°, and the filtrate was evaporated *in vacuo* to remove water and excess hydrogen bromide. Treatment of the crude hydrobromides so formed with hydrogen bromide acceptors under the conditions given in Table II led to crude products which were isolated and purified as shown.

If the hydrolysis of VIII or XII was stopped after 10–30 min., the precipitate present proved to be XI or XIII, respectively, *i.e.*, only the ester group was selectively hydrolyzed first. The precipitates were recovered and purified as shown in Table II.

Analytical data for the products in Table II are listed in Table III; infrared in Table IV.

Acknowledgment.—This work was supported in part by the Office of Naval Research. Analytical work was performed by our analytical department, including the interpretation of the infrared spectra by Miss Ruth A. Kossatz. Miss Barbara I. D'Iorio assisted in part of the experimental work.

A New Synthesis of 1,1,4,4-Tetramethoxybutyne-2

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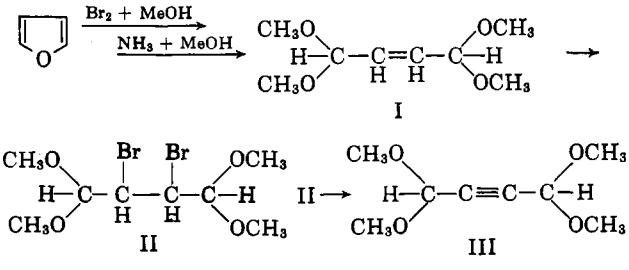
During a program initiated to investigate alkoxy-substituted unsaturates, tetramethoxybutyne was synthesized. This compound had previously been prepared by Wohl[1] *via* the reaction of acetylene di-Grignard and methyl orthoformate. This route has very stringent reaction conditions, and generally requires extreme care during work-up before isolation of the final product. The new synthesis has the advantage of a simplified preparation in addition to a crystalline intermediate which can be isolated and used as a check on the preceding steps.

The precursor 1,1,4,4-tetramethoxybutene-2 (I) was prepared by brominating furan with one equivalent of bromine in methanol solution to give the 2,5-dimethoxydihydrofuran. Without isolating this intermediate the furan ring was opened by ammonolysis[2] to give the tetramethoxybutene. Bromination of the butene gave a crystalline dibromo derivative II melting at 99–99.5°.



Dehydrobromination of the crystalline dibromo compound could theoretically lose two moles of hydrogen bromide, to give either the butyne, butadiene, or allene derivative. Using potassium *t*-butoxide in *t*-butyl alcohol only the butyne III was isolated. (Alcoholic potassium hydroxide gave the same results.) The partially dehydrobrominated product, 1,1,4,4,-tetramethoxy-2-bromobutene-2, was not found as a reaction product.

A sample of the butyne prepared by this new method was compared with that produced by Wohl's synthesis[1], and they were found to be identical.

(1) A. Wohl and E. Bernreuther, *Ann.*, **481**, 1 (1930).

(2) A. Boehringer, E. Boehringer, I. Liebrecht, and J. Liebrecht, British Patent 747,281 (January 25, 1954).