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A GENERAL, HIGHLY EFFICIENT SYNTHESIS OF ACETYL AMINO ACID ETHYL ESTERS

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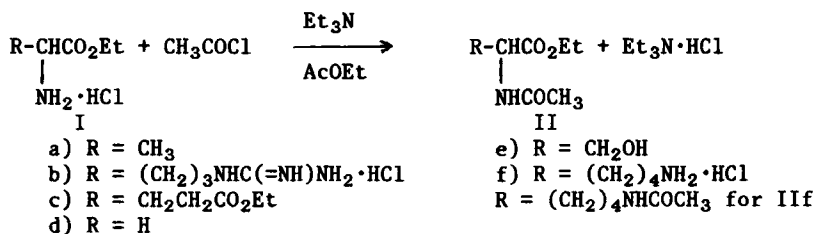
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A GENERAL, HIGHLY EFFICIENT SYNTHESIS OF ACETYL AMINO ACID ETHYL ESTERS

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It was of interest to have a more practical method for the preparation of N-acetyl amino acid ethyl esters. Thus, a very practical and economical method has been developed for the preparation of amino acid ethyl esters¹ and the N-acetyl ester of L-tyrosine.² The present work extends the previously reported method² to six additional amino acid ethyl esters of different classes thus demonstrating the general applicability of this method.



The procedure is essentially that of the procedure B outlined for the synthesis of N-acetyl ethyl ester of L-tyrosine,² using stoichiometric amounts of acetyl chloride and appropriate amounts of triethylamine, sufficient to bind free hydrogen chloride. Purification of the acetylated esters depends upon the nature of the product. Solid products such as the acetyl esters of lysine and tyrosine were purified by recrystallization; oily compounds were purified by fractional distillation. The acetyl ester of L-arginine (IIb) is very hygroscopic, and sensitive to heat. It was purified by dissolution in isopropanol or ethyl alcohol and followed by

precipitation with ether. The crude acetylated esters were sufficiently pure for practical purposes. Since the acetylated ethyl ester of arginine (IIb) and lysine (IIf) are not known, detailed procedures of their syntheses are described. Only data essential to establish the identity of known compounds IIa, IIc, IID, and IIe^{3,4} are given. In general, the yields reported here are improved by 15-20% and this procedure avoids possible decomposition⁵ and racemization.^{6,7}

The mass spectrum of N^{α,ε}-diacetyl-L-lysine ethyl ester (Table I) exhibited 16 major peaks, with relative abundance of the ions of more than 5%. Each peak is labeled by elemental composition, as obtained from the computer.

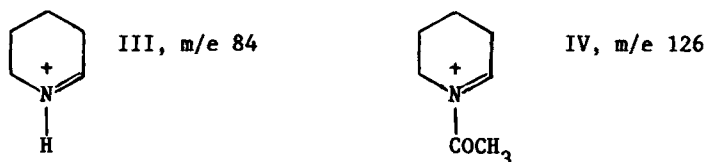
TABLE I - Mass Spectrum of N^{α,ε}-Diacetyl-L-Lysine Ethyl Ester

Mass	Relative abundance %	Elemental composition			
		C	H	N	O
258.2598	5.33	12	21	2	4
215.1392	6.45	10	19	2	3
212.1132	8.94	10	16	2	3
185.1299	13.44	9	17	2	2
156.1020	14.68	7	13	1	2
141.1025	5.14	7	13	2	1
126.0911	100.00	7	12	1	1
114.0934	16.85	6	12	1	1
84.0828	84.82	5	10	1	0
72.0445	10.65	3	6	1	1
56.0457	14.27	3	6	1	0
44.0461	10.79	2	6	1	0
43.0151	40.64	2	3	0	1
30.0339	29.30	1	4	1	0
29.0386	7.88	2	5	0	0
28.0182	8.55	1	2	1	0

The purity of this compound becomes apparent from the peak with m/e 258.1598 since the calculated molecular weight is 258.25. The spectrum of this compound resembles that of the ethyl ester of lysine,⁸ which exhibits a characteristic peak at m/e 84. This peak has been also observed in the spectrum of lysopine,⁹ which is N^α-substituted derivative of lysine, occur-

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ring in tobacco. $N^{\alpha,\epsilon}$ -diacetyl-L-lysine ethyl ester exhibits the same peak with relative intensity of 84.82% and, in addition, a stronger peak is exhibited with m/e 126.0911, and relative intensity of 100%. Both fragments are represented by the ions III and IV, which may be taken as the



most characteristic fragments of the mass spectrum of $N^{\alpha,\epsilon}$ -diacetyl-L-lysine ethyl ester. Most probably, they are formed via a rearrangement postulated by Biemann et al.⁸ Mass spectra are not suitable for determination of the structure of arginine, especially of its salts and esters.¹⁰

EXPERIMENTAL

The ¹³C-NMR-spectra were determined on a JEOL FX60Q 15.04 MHz spectrometer, in 79% H₂O, 20% D₂O and 1% p-dioxane, as internal standard; in a 10 mm tube, at pH 1.8, c. 300 mg/ml. The spectrum was obtained with a 58° pulse, a repetition rate of 3.5 sec, over a 4000 Hz spectral width with complete proton decoupling. The high resolution mass spectra were obtained on the Varian¹² spectrometer MAT 311A, interfaced to a data processing computer, "Incos 2300", at the following conditions: $M/\Delta M = 10,000$, $E_{fill} = 70$ ev, scanning speed 25 sec, range m/e 12-700.

N-Acetyl-dl-alanine ethyl ester (IIa), bp 95-97°/1-2 mm, 97% yield.

Anal. Calcd. for C₇H₁₃NO₂: N, 8.79. Found: N, 8.86

N-Acetyl-dl-glutamic acid ethyl ester (IIc), bp 141-143°/2 mm, 95% yield.

Anal. Calcd. for C₁₁H₁₉NO₅: N, 5.70. Found: N, 5.50

N-Acetyl-dl-glycine ethyl ester (II d), bp 107°/2 mm; mp 48°, 95% yield.

Anal. Calcd. for C₆H₁₁NO₃: N, 9.64. Found: N, 9.58

N-Acetyl-dl-serine ethyl ester (IIe), bp 155-160°/1-2 mm, 93% yield.

Anal. Calcd. for C₇H₁₃NO₄: N, 7.99. Found: N, 7.85

N^α-Acetyl-L-arginine ethyl ester monohydrochloride (IIb).-A mixture of 27.52 g (0.1 mole) of L-arginine ethyl ester dihydrochloride,¹ 100 ml of

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ethyl acetate, 150 ml of glacial acetic acid, and 20.24 g (0.7 mole) of triethylamine in a 500 ml three-necked reaction flask, equipped with a condenser, stirrer, and addition funnel, was placed in a silicon bath at about 45° and stirred for about 15 min. Then a solution of 7.86 g (0.1 mole) of acetyl chloride in 50 ml ethyl acetate, was added dropwise. After completion of the addition (about 30 min), reaction mixture was stirred at ~45° for an additional 30 min, then concentrated to dryness at 25°/0.1 mm. The residue was extracted with 200 ml of ethanol, decolorized with activated carbon, and filtered. Absolute ether (250 ml) was added to the filtrate and the precipitate was separated by decantation and dried for about 20 h at 25°/0.1 mm, whereupon the theoretical amount (28.28 g) of a highly hygroscopic product was obtained. This material could be handled only under nitrogen. About 5 g of this material was dissolved in 50 ml isopropanol, filtered with suction, and 50 ml of absolute ether was added to the filtrate. The precipitate was separated by decantation, dried for about 20 h at 25°/0.1 mm, giving 3.08 g (75%) of IIb, mp 69-72° (vac. sealed capillary), softening at ~60°, $[\alpha]_D^{25} = -9.15$ (c. 3%, H₂O).

Anal. Calcd. for C₁₀H₂₁ClN₄O₃: C, 42.77; H, 7.54; N, 19.94; Cl, 12.62

Found: C, 42.45; H, 7.38; N, 19.81; Cl, 12.73

IR (KBr): 3320-3130, 2920, 1730, 1660-1630, 1540-1520, 1435, 1370, 1220-1180 and 1130 cm⁻¹. ¹³C NMR (relative to TMS): δ 176.3, 174.9, 157.6, 67.39 (ref., p-dioxane). 63.4 (CH₂ of the ester). 58.3 (CH₂ of the hydr. EtOH), 53.4, 41.4, 28.5, 25.2, 23.59 (CH₃ of hydr. EtOH), 14.2 (CH₃ of the ester). The chemical shifts assignments were made using the shifts of L-arginine monohydrochloride¹¹ as a model compound.

N^α-Acetyl-L-arginine.-A mixture of 17.42 g (0.1 mole) of L-arginine, 100 ml glacial acetic acid and 0.1 mole (10.20 g) of acetic anhydride in a 500 ml reaction flask, equipped with a stirrer and condenser was heated for 2 h at

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105°, with occasional stirring. It was allowed to stand at room temperature overnight and 300 ml of ether was added. The precipitated product was separated by decantation and dried for several hours at 56°/0.1 mm, whereupon 21.92 g of a white amorphous material was obtained. The solid was then dissolved in 100 ml of ethanol, refluxed for about 5 min and allowed to stand at room temperature for about 5 h. The precipitated material was filtered by suction, under nitrogen, and dried for 4 h at 56°/0.1 mm, giving 14.70 g (68%) of white crystalline product, mp 261-263°, $[\alpha]_D^{25} = +9.73$ (c. 3%, H₂O).

Anal. Calcd. for C₈H₁₆N₄O₃: C, 44.43; H, 7.45; N, 25.91

Found: C, 44.36; H, 7.43; N, 25.66

IR (KBr): 3320-3220, 3060-3040, 2940, 1640, 1565-1555, 1445, 1290, and 950 cm⁻¹. ¹³C-NMR, (pH 5.0, c. 300 mg/ml) δ 179.4 (COOH), 174.3 (COCH₃), 157.6, 67.4 (ref., p-dioxane), 53.3, 41.4, 28.5, 22.4, and 21.1.

About 0.025 mole (5.4 g) of N^α-acetyl-L-arginine was esterified as previously described.¹ At the end of the reaction, the reaction mixture was concentrated to about 50 ml, and the product precipitated with 100 ml of ether. The precipitated product was separated by decantation and dried for about 4 h at 56°/0.1 mm, yielding 7.05 g (100%) of IIb. The identity of this compound was confirmed by elemental analyses, IR and ¹³C-NMR spectra. N^{α,ε}-Diacetyl-L-lysine ethyl ester IIc.-A mixture of 24.70 g (0.1 mole) of L-lysine ethyl ester dihydrochloride,¹ 300 ml of ethyl acetate and 0.40 mole (40.50 g) of triethylamine in a 500 ml three-neck reaction flask, equipped with a condenser and stirrer and immersed in a silicon bath at about 40°. To the reaction mixture was added, dropwise, with stirring, 0.2 mole (15.70 g) acetyl chloride, dissolved in 100 ml of ethyl acetate. In about 2-h the addition was completed. The reaction mixture was allowed to react for additional 2 h at room temperature and then was filtered. The

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residue was washed with warm ethyl acetate, the filtrates were combined and concentrated in vacuum at room temperature until a thick sirup was obtained. This was dried for several hours at 25°/0.1 mm, whereupon 25.5 g (98.8% yield) of a yellowish wax-like product was obtained. This material was extracted with hot toluene, recrystallized from toluene (75 ml/g) and dried for few hours at 56°/0.1 mm, giving 15.5 g (60.1%) of slightly yellowish product, mp 87-87.5°, $[\alpha]_D^{25} = -25.83$ (c 3, H₂O).

Anal. Calcd. for C₁₂H₂₂N₂O₄: C, 55.79; H, 8.91; N, 10.85

Found: C, 55.45; H, 8.76; N, 10.65

IR (KBr): 3350, 2940, 2875, 1750, 1640, 1550, 1450, 1375, 1350, 1280, 1240, 1220, 1120, 1045, 1010, 970, 865, 775, 740, and 710 cm⁻¹.

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