Synthesis and NMR Spectroscopic Studies of Optically Active Derivatives of γ-Aminobutenoic Acids and 2-Amino-pyrrolin-4-ones

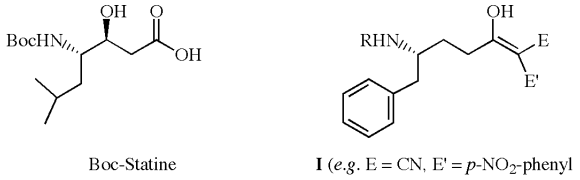
Margarita Petroliagi and Olga Igglessi-Markopoulou*

Laboratory of Organic Chemistry, Department of Chemical Engineering,
National Technical University of Athens, Zografou Campus, 157 73 Athens, GREECE
Received September 5, 2000

An efficient method for the preparation of optically active derivatives of γ-amino-butenoic acids and their cyclic derivatives, 2-amino-pyrrolin-4-ones, from α-amino acids is described. Partial racemization accompanies the formation of initial unsaturated γ-amino-β-hydroxy esters **5-8**, as determined by chiral HPLC.

J. Heterocyclic Chem., **38**, 917 (2001).

Recent synthetic work and structure-activity studies on β-hydroxy-γ-amino acids, analogues of statine, have revealed that these compounds are of increased pharmacological significance due to their participation in the bioactivity of peptides and their ability to act as selective renin inhibitors [1]. Especially, the difunctionalised enols of type **I** (Figure I) possessing topographical similarities with Boc-statine, have attracted much attention after clinical evaluation as they constitute potent, powerful inhibitors against HIV protease [2].



Boc-Statine **I** (*e.g.* E = CN, E' = *p*-NO_2-phenyl

Figure I

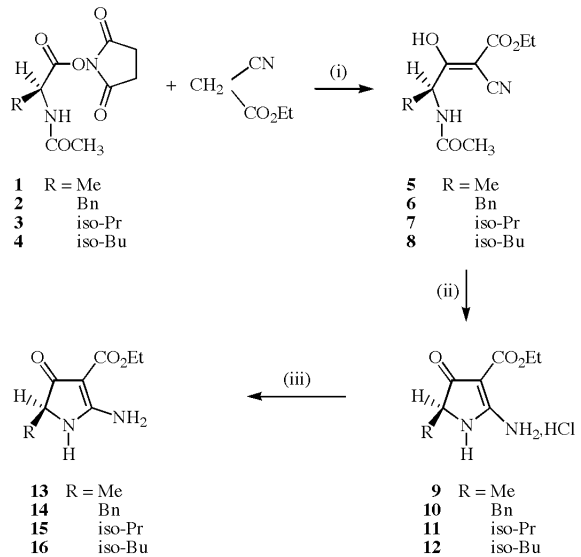
A key feature of rationally designed HIV inhibitors has been the introduction of substituents to these derivatives that mimic natural substrate side chains, whilst retaining or improving activity against both the enzyme and the virus. Extensive screening and modeling studies have revealed that the presence of two electron-withdrawing substituents at the positions E,E' modulate the electron density of the electrophilic center at the vinylic position that interacts with the nucleophilic groups at the active site of enzymes, favoring in this way enzyme-inhibitor interaction.

In the light of this relevance of β-hydroxy-γ-amino acids the development of efficient methods for their asymmetric construction is of great importance to organic synthesis in general and to natural product and medicinal chemistry in particular. G.Sauvé and co-workers [2] have reported a synthetic sequence to optically active difunctionalised enols of type **I** (Figure I) which involves the condensation of an appropriate active methylene compound with an activated acyl-imidazole intermediate. Another strategy for the construction of compounds of this class involves the *C*-acylation reactions of ethyl cyanoacetic esters with *N*-hydroxysuccinimide esters of *N*-substituted-α-amino acids, as it has been recently reported by our laboratory [3].

Another important class of potential medicinal agents that have been identified as efficacious antiviral drugs are the nitrogen heterocyclic compounds possessing the pyrroline ring system. Especially, the derivatives of 2-amino-pyrroles exhibit antiallergic, local anaesthetic, antiarrythmic, hypotensive and anticonvulsant properties [4]. Recently, these compounds have been used as important heterocyclic building blocks of antibiotics for the treatment of osteoporosis, breast cancer and cardiovascular disorder, *e.g.*, thrombosis [5]. Analogues of 2-amino-pyrroles have been synthesized by a standard Dieckmann condensation using ethyl α-cyano-γ-chloroacetoacetates as precursors, either by a thermal condensation of α-aminoketones with *t*-butyl-cyanoacetate, or by reaction of primary and secondary amines with oxazolin-2-ylidene-malonitriles [6].

In continuation of our studies on the use of *N*-hydroxysuccinimide esters of *N*-acetyl-α-amino acids [7], as precursors for the synthesis of compounds with interesting biological properties, we propose here an efficient methodology for the construction of optically active 4-amino-3-hydroxy-2-cyano-2-butenoates **5-8** as useful synthons for the synthesis of

Scheme I



1 R = Me, **2** Bn, **3** iso-Pr, **4** iso-Bu

5 R = Me, **6** Bn, **7** iso-Pr, **8** iso-Bu

13 R = Me, **14** Bn, **15** iso-Pr, **16** iso-Bu

9 R = Me, **10** Bn, **11** iso-Pr, **12** iso-Bu

i) NaH/THF; ii) 8% HCl/EtOH; iii) NaOH 1%

chiral 2-amino-pyrrolin-4-ones **9-16**. For our starting reagents, we have chosen *N*-hydroxysuccinimide esters of four different optically active *N*-acetyl-α-amino acids (L-alanine, L-phenylalanine, L-valine, L-leucine). Employment of the anion of ethyl cyanoacetate (sodium hydride, tetrahydrofuran, 0 °C) with *N*-hydroxysuccinimide esters **1-4**, the novel optically active γ-acetamino-β-hydroxybutenoates **5-8** have been formed (Scheme I).

In a typical *C*-acylation reaction 3 equivalents of the ethyl cyanoacetate were treated with 2 equivalents of sodium hydride in tetrahydrofuran at 0 °C. After stirring of the reaction mixture for 1 hour, *N*-hydroxysuccinimide ester **1-4** was added and stirring was continued for further 3hours, at 0 °C. After workup of the reaction mixture, as it is described in the experimental section, the difunctionalised enols **5-8** were isolated without further cylclization in good yields. The enantiomeric ratio, e.r., of the compounds was 78-94% (Table 1), as determined by means of HPLC using a chiral stationary phase.

tions. Any effort to determine the enatiomeric ratio of these compounds, by means of HPLC were unsuccessful.

The structure of the newly prepared *C*-acylation compounds **5-8** and 2-aminopyrrolin-4-ones **13-16** has been elucidated using NMR and IR spectroscopy. The difunctionalised enols **5-8** can occur in two enolic forms, *Z* and *E*, from which the *Z*-enol form should be the most stable due to the presence of intramolecular hydrogen bonding (Figure II). The ^{1}H and ^{13}C NMR spectra of these compounds confirm their existence, in deuteriochloroform solution, in

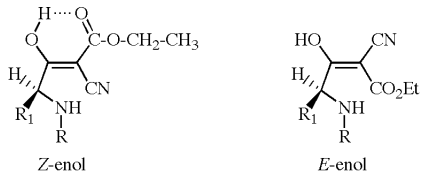


Figure II

Table 1

Physical properties of the C-acylation compounds **5-8**

Compound	Enant. ratio(t, min) [a]	$[\alpha]_D$ [b]	mp (°C)	Yield(%)	e.e
5	84 (6.22) : 16(7.83)	+21.4 (c1, MeOH)	128-132	50	68
6	78 (5.82) : 22 (7.62)	+130.5 (c1.32, MeOH)	164-165	77	56
7	94 (6.00) : 6(7.57)	+8.2 (c1.05, $CHCl_3$)	102-105	45	88
8	92 (5.88) : 8(7.60)	+28.4 (c1.3, MeOH)	89-93	65	84

[a]The enantiomeric ratios were determined by HPLC analysis with a CHIRALPAK AS column (4.6x250mm), [245nm, 0.55 ml/min, ethanol-hexane (90:10)]; [b]Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.

An important feature for the proposal methodology has been the use of *N*-hydroxysuccinimide esters of *N*-acetyl-L-amino acids as acylating agents. These esters are stable, can be stored for a long time and are easily prepared, therefore are useful precursors for the synthesis of optically active functionalized enols.

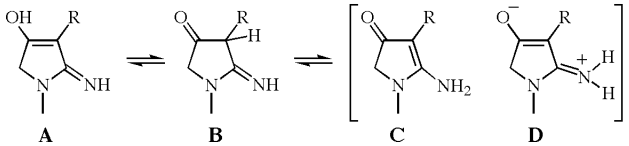
Then, our attention was concentrated on the use of the *C*-acylation compounds **5-8** as synthons for the construction of novel optically active 2-amino-pyrrolin-4-ones. As it has been reported, nitrogen heterocycles possessing one or more stereogenic centers constitute important subunits of natural products which exhibit a broad range of biological activities [8]. Ring closure to 2-amino-pyrrolin-4-ones **9-12** was achieved by refluxing the *C*-acylation compounds **5-8** in a solution of 8% hydrochloric acid in ethanol for 3 hours. When the reaction mixture was concentrated *in vacuo*, the hydrochloride salts of 2-amino-pyrrolin-4-ones **9-12**, with a small amount of the corresponding amines, were obtained.

Treatment of the hydrochlorde salts **9-12** with a solution of 1% sodium hydroxide at 0 °C for 1 hour, the free enamines, 2-amino-3-ethoxycarbonylpyrrolin-4-ones **13-16**, showed an optical rotation confirming that the pyrrolinone nucleus possess a stereogenic center, under these experimental conditions.

enolic form (Tables 2,3). In addition, due to the electron-withdrawing character of CN group, the enol population is increased in these compounds and thus the OH chemical shift is decreased (δ_H ~13-14 ppm) [9].

The 2-amino-pyrrolin-4-ones can occur in the following tautomeric forms AB[C/D] (Scheme II) [3c].

Scheme II

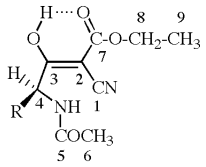


The ^{1}H NMR spectra of 2-amino-pyrrolin-4-ones **13-16** in hexadeuteriodimethylsulfoxide solution confirmed that the predominant form should be the tautomer C, as there is not any characteristic resonance of a methine proton at C-3 corresponding to the tautomer B, or any signals of OH group corresponding to the tautomer A (Tables 4,5). The signals of $-NH_2$ appear upfield and are exchangeable with D_2O.

The IR spectra of the *C*-acylation compounds **5-8** show absorptions bands at 3295-3210 and 2220-2210 cm^{-1}

Table 2

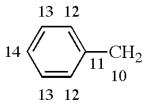
^{1}H NMR Spectra of Compounds **5-8** (300MHz, $CDCl_3$)



Compound	R	$CO_2CH_2CH_3$	C*H*-R	$COCH_3$	$CO_2CH_2CH_3$	C*H*R	NH	OH
5	CH_3	1.31 (3H, t, J 6.8)	CH_3 1.53 (3H, d, J 7.3)	1.98 (3H, s)	4.29 (2H, q, J 6.8)	4.83 (1H, m)	6.60 (1H, bs)	13.75 (1H, br)
6	$CH_2C_6H_5$	1.35 (3H, t, J 7.3)	$CH_2C_6H_5$ 3.18, 3.04 (1H, dd, J 6, 8.4) 3.13, 2.99 (1H, dd, J 5.7, 8.4) C_6H_5 7.20-7.35 (5 H, m)	1.96 (3H, s)	4.32 (2H, q, J 6.8)	5.14 (1H, dd, J 7.3)	5.92 (1H, bs)	13.90 (1H, br)
7	$CH(CH_3)_2$	1.36 (3H, t, J 6.8)	$CH(CH_3)_2$ 1.03(6 H, d, J 6.59) $CH(CH_3)_2$ 2.09-2.16 (1H, m)	2.05 (3H, s)	4.34 (2H, q, J 7.3)	4.71 (1H, t, J 8.0)	5.95 (1H, bs)	13.94 (1H, br)
8	$CH_2CH(CH_3)_2$	1.34 (3H, t, J 7.33)	$CH_2CH(CH_3)_2$ 0.95,0.98(6H, dd, J 4.4) CH_2CH 1.58-1.72 (3H, m,)	2.02 (3H, s)	4.32 (2H, q, J 7.3)	4.84-4.91 (1H, m)	6.16 (1H, bs)	14.24 (1H, br)

Table 3

^{13}C NMR Spectra of Compounds **5-8** ($CDCl_3$)

Compound	**R**	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13	C-14
5	CH_3 (10)	113.49	78.97	190.31	48.12	170.28	22.12	170.44	62.62	13.65	17.53	------	------	------	------
6		113.40	80.80	188.32	53.61	169.83	22.49	170.50	62.87	13.79	38.49	135.09	129.19	128.97	127.65
7	$CH(CH_3)_2$ (10 11,12)	113.74	80.95	188.53	57.60	170.13	22.24	170.81	62.60	13.61	30.81	18.73 18.26		------	------
8	$CH_2CH(CH_3)_2$ (10 11 12,13)	113.72	72.62	190.09	51.06	170.36	21.39	170.49	62.77	13.82	41.39	24.77	22.71 22.51		------

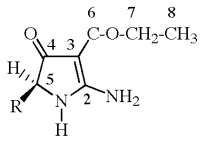
which are attributed to the NH and C≡N stretching, respectively. In the carbonyl region, only the compounds **6** and **8** exhibit absorption band for the CO group of the keto form at 1720–1710 cm^{-1}, whereas all the *C*-acylation compounds **5-8** show a characteristic absorption band at 1665-1640 cm^{-1} for the CO group of the enol form of the β-dicarbonyl system CO-CH-CO↔C(OH)=C-CO. The band at 1585 cm^{-1} is attributed to the carbon-carbon double bond. These results indicate that the *C*-acylation compounds **6** and **8** exist as a mixture of the keto- and enol- form, whereas the *C*-acylation compounds **5** and **7** predominate in their enolic form, in the solid state.

In the work described above we have developed a concise and versatile approach to optically active cyano derivatives of β-hydroxy-γ-amino acids and we have been innovative in the determination of their enantiomeric purity as the enantiomeric ratios of such difunctionalised enols are reported for first time. The merits of this synthetic route are the mild reaction conditions, the short reaction times, the high yields in which the products were isolated with partial racemization. The procedure is directed towards extending the previous one reported recently by our laboratory [3] as it includes modifications on the reaction conditions and is applied on the preparation of more aminoacids derivatives. Furthermore, it extends the usefulness of novel synthesized difunctionalised enols as precursors for the construction of optically active 2-amino-pyrrolin-4-ones whose enantiomeric ratio determination is under investigation.

In conclusion, the reported novel class of optically active difunctionalised enols and aminopyrrolinones may serve as useful probes for studying structure-activity relationships in medicinal chemistry.

Table 4

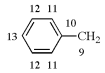
^{1}H NMR of Compounds **13-16** (300MHz, [$^2H_6$]DMSO)



Compound	OCH_2CH_3	OCH_2CH_3	C-*R*	C*H*R	NH	NH_2
13	1.16	4.04	CH_3	3.5	7.38	7.99
R=CH_3	(3H, t, J 7.0)	(2 H, q, J 6.8)	1.09 (3 H, d, J 6.8)	(1 H, q, J 6.8)	(1 H, bs)	(2 H, bs)
14	1.15	4.03	$CH_2C_6H_5$	3.79-3.83	7.48	C_6H_5 and NH_2
R=$C_6H_5CH_2$	(3H, t, J 7.0)	2 H, bq, J 6.8)	2.57, 2.62 (1H,dd, J 5.7, 2.4) 2.97, 3.02 (1H, dd, J 6.3, 3.0) C_6H_5 and NH_2 7.18-7.28 (~7 H, m)	(1 H, m)	(1 H, bs)	7.18-7.28 (~7 H, m)
15	1.15	3.98-4.09	$CH(CH_3)_2$	3.41	7.68	7.4
R=$(CH_3)_2CH$	(3H, t, J 7.0)	(2 H, m)	0.66, 0.92 (3H, dd, J 6.8) $CH(CH_3)_2$ 1.94-2.02 (1 H, m)	(1 H, d, J 3.4)	(1 H, bs)	(2 H, bs)
16	1.15	4.04	$CH_2CH(CH_3)_2$	3.49-3.53	7.76	7.39
R=$(CH_3)_2CHCH_2$	(3H, t, J 7.0)	(2H, q, J 7.3)	0.86 (6 H, d, J 6.6) $CH_2CH(CH_3)_2$ 1.40-1.76 (3 H, m)	(1 H, m)	(1 H, bs)	(2 H, bs)

Table 5

^{13}C NMR of Compounds **14-16** ([$^2H_6$]DMSO)

Compound	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9	C-10	C-11	C-12	C-13
14 R= 	164.99	85.84	190.17	62.41	169.76	57.73	14.53	37.24	137.76	129.39	128.29	126.42
15 R= $(CH_3)_2CH$ 11, 10 9	165.01	86.13	190.79	66.41	170.40	57.71	14.50	29.36	19.19 15.43		------	------
16 R= $(CH_3)_2CHCH_2$ 12, 11 10 9	165.18	85.41	191.56	60.14	169.73	57.72	14.54	41.05	24.48	23.31 21.69		------

EXPERIMENTAL

Melting points were determined on a Gallenkamp MF13-595 melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin Elmer 267 spectrometer. The ^{1}H nmr spectra were recorded on a Varian Gemini-2000 300 MHz spectrometer; chemical shifts are quoted in ppm (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad); J values are given in Hz. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter, at 25 °C. The Mass spectra were recorded on a VG 7070 E/DEC VAX 4000,60 Instrument using Fast Atom Bombardment (FAB), University of Liverpool. HPLC has been carried out on a Varian 2501, using a packed column, [CHIRALPAK AS (4.6x250mm)]. The mobile phase was ethanol-hexane (90:10). Elemental analyses were obtained from the University of Liverpool, Chemistry Department. Solvents and reagents were dried or purified according to the procedure described by Perrin and Armarego [10].

Preparation of Optically Active *N*-Acetyl-α-amino Acids.

The *N*-acetyl-L-alanine and *N*-acetyl-L-phenylalanine were commercially available. The requisite *N*-acetyl-L-leucine and L-valine were prepared using the method of H. D. DeWitt and A. W. Ingersoll [11].

General Procedure for the Synthesis of Optically Active *N*-Hydroxysuccinimide Esters of *N*-Acetyl-α-amino Acids **1-4**.

The requisite *N*-hydroxysuccinimide esters of *N*-acetyl-α-amino acids **1-4** were prepared according to a method which has been recently reported [7], with minor modifications: the mixture of *N*-acetyl-α-amino acid (50 mmoles), *N*-hydroxysuccinimide (50 mmoles) and *N,N'*-dicyclohexylcarbodiimide (50 mmoles) in tetrahydrofuran (160 ml) was stirred at 0 °C. After the filtration of *N,N'*-dicyclohexylurea, the solution was concentrated *in vacuo* giving either a solid or an oily product.

N-Hydroxysuccinimide Ester of *N*-Acetyl-L-alanine (**1**).

According to the previous procedure compound (**1**) was obtained after concentration *in vacuo* as a solid, mp 119-122 °C (65%), $[\alpha]_D$

+71.5 (c4.0, MeOH); ^{1}H nmr (deuteriochloroform): δ 1.58 (3 H, d, *J* = 7.3, $CHCH_3$), 2.03 (3 H, s, $COCH_3$), 2.84 (4 H, s, $CO(CH_2)_2CO$), 4.99 (1 H, q, *J* = 7.3, CHCO) and 6.09 (1 H, br, NH).

N-Hydroxysuccinimide Ester of *N*-Acetyl-L-phenylalanine (**2**).

According to the previous procedure the title compound was obtained as a solid, mp 152-154 °C (85%), $[\alpha]_D$ -39 (c1.0, MeOH); ^{1}H nmr (deuteriochloroform): δ 1.94 (3 H, s, $COCH_3$), 2.79 (4 H, s, $CO(CH_2)_2CO$), 3.18, 3.30 (2 H, 2dd, *J* 5.7 and 6.0, $CH_2C_6H_5$), 5.24 (1 H, m, CHCO), 6.11 (1 H, br, NH) and 7.22-7.34 (5 H, m, C_6H_5).

N-Hydroxysuccinimide Ester of *N*-Acetyl-L-valine (**3**).

According to the previous procedure the title compound was obtained as a solid, mp 136-140 °C (84%), $[\alpha]_D$ -55.43 (c1.6, MeOH); ^{1}H nmr (deuteriochloroform): δ 1.06 and 1.03 [6 H, two d, *J* 2.1, $CH(CH_3)_2$], 2.05 (3 H, s, $COCH_3$), 2.32 [1 H, m, $CH(CH_3)_2$], 2.83 (4 H, s, $CO(CH_2)_2CO$), 4.92 (1 H, d, *J* 5.1, CHCO) and 6.09 (1 H, br, NH).

N-Hydroxysuccinimide Ester of *N*-Acetyl-L-leucine (**4**).

According to the previous procedure the title compound was obtained as a waxy solid (85%), $[\alpha]_D$ -18.94 (c1.28, MeOH); ^{1}H nmr (deuteriochloroform): δ 0.93 [6 H, m, $CH(CH_3)_2$], 1.74 (3 H, m, CH_2CH), 2.00 (3 H, s, $COCH_3$), 2.79 [4 H, s, $CO(CH_2)_2CO$], 4.97 (1 H, m, CHCO) and 6.47 (1 H, br, NH).

General Method for the Preparation of Compounds **5**-**8**.

The ethyl cyanoacetate (26.4 mmoles) was added dropwise to a suspension of sodium hydride (55-60 % sodium hydride in oil; 17.6 mmoles) in anhydrous tetrahydrofuran (20 ml) and the thick slurry thus formed was stirred at 0 °C for 1 hour. The *N*-hydroxysuccinimide ester of *N*-acetyl-α-amino acid **1**-**4** (8.8 mmoles) was then added to the mixture and stirring continued for 3 hours, at 0 °C. The reaction mixture was concentrated *in vacuo* and the solid obtained was diluted in water and washed with diethyl ether. The aqueous layer was separated, acidified with 10% hydrochloric acid in an ice-water bath giving a solid that was washed with light petroleum ether.

Ethyl-4-acetylamino-2-cyano-3-hydroxypent-2-enoate (**5**).

According to the previous procedure the title compound (**5**) was obtained as a solid (1.9 g, 50%) mp 128-132 °C (from chloroform-light petroleum ether), $[\alpha]_D$ +21.4 (c1.0, MeOH); ir(Nujol): 3280s,sh (NH), 2210m,sh (CN), 1640m,br (CO ester, enol form), 1585w,br (C=C), 1545m,br (amide II) cm^{-1}; ^{1}H nmr (deuteriochloroform) see Table 2; ^{13}C nmr (deuteriochloroform) see Table 3; ms: m/z 226 (M^+, 4.71%), 184 (10.03), 112 (6.56), 86(100), 44(98.15).

Ethyl 4-Acetylamino-2-cyano-3-hydroxy-5-phenylpent-2-enoate (**6**).

According to the previous procedure the title compound was obtained as a solid (0.95 g, 77 %) mp 164-165 °C (from chloroform-light petroleum ether), $[\alpha]_D$ +130.5 (c1.32, MeOH); ir(Nujol): 3295s,sh (NH), 2220m,sh (CN), 1720w,br (CO ester, keto form), 1650m,br (CO ester, enol form), 1585m,br (C=C), 1530m,br (amide II) cm^{-1}; ^{1}H nmr (deuteriochloroform) see Table 2; ^{13}C nmr (deuteriochloroform) see Table 3; ms: m/z 302 (M^+, 1.40%), 256(10.70), 243 (22.61), 169(100), 43(79.79).

Anal. Calcd. for $C_{16}H_{18}O_4N_2$: C, 63.56; H, 6.00; N, 9.27. Found C, 63.42; H, 6.02; N, 9.27.

Ethyl 4-Acetylamino-2-cyano-3-hydroxy-5-methylhex-2-enoate (**7**).

According to the previous procedure the title compound was obtained as a solid (0.89 g, 45%) mp 102-105 °C (from chloroform-light petroleum ether), $[\alpha]_D$ +8.17 (c1.05, $CHCl_3$); ir(Nujol): 3240m,br (NH), 2218s,sh (CN), 1655w,br (CO ester, enol form), 1585w,br (C=C), 1540w,br (amide II) cm^{-1}; ^{1}H nmr (deuteriochloroform) see Table 2; ^{13}C nmr (deuteriochloroform) see Table 3; ms: m/z 254 (M^+, 0.19), 211 (2.72), 183 (5.38), 139(52.14), 68(100), 43(30).

Anal. Calcd. for $C_{12}H_{18}O_4N_2$: C, 56.88; H, 7.13; N, 11.01. Found C, 56.83; H, 7.12; N, 11.04.

Ethyl 4-Acetylamino-2-cyano-3-hydroxy-6-methyl-2-heptenoate (**8**).

According to the previous procedure the title compound was obtained as a solid (1.54 g, 65%) mp 89-93 °C (from chloroform-light petroleum ether), $[\alpha]_D$ +28.4 (c1.3, MeOH); ir(Nujol): 3210s,sh (NH), 2220s,sh (CN), 1710w,sh (CO ester, keto form), 1655s,sh (CO ester, enol form), 1590m,br (C=C), 1545s,sh (amide II) cm^{-1}; ^{1}H nmr (deuteriochloroform) see Table 2; ^{13}C nmr (deuteriochloroform) see Table 3; ms: m/z 268 (M^+, 35%), 269 (21), 225 (100).

Anal. Calcd. for $C_{13}H_{20}O_4N_2$: C, 58.19; H, 7.51; N, 10.44. Found C, 58.12; H, 7.52; N, 10.49.

General Method for the Preparation of Compounds **9**-**12**.

The *C*-acylation compound **5**-**8** (14 mmoles) was added in a solution of 8% hydrogen chloride in ethanol, prepared from the addition of acetyl chloride (11 ml) in anhydrous ethanol (113 ml). The reaction mixture was refluxed for 3 hours and set aside overnight at room temperature. Then it was evaporated *in vacuo* to give the hydrochloric salt of compounds **9**-**12**.

General Method for the Preparation of Compounds **13**-**16** as Free Amines.

The Hydrochloric salt **9**-**12** (1.14 mmoles) was added to a solution of sodium hydroxide 1% (3 ml) and the reaction mixture was stirred for 1 hour at 0 °C. The solid product so formed was isolated by filtration.

2-Amino-3-ethoxycarbonyl-5-methylpyrrolin-4-one (**13**).

According to the previous procedure the title compound was obtained after extraction of the aqueous solution with ethyl acetate as a waxy solid (0.17 g, 35%), $[\alpha]_D$ +10 (c0.2, MeOH); ^{1}H nmr (dimethyl-d_6 sulfoxide) see Table 4.

2-Amino-3-ethoxycarbonyl-5-benzylpyrrolin-4-one (**14**).

According to the previous procedure the title compound was obtained as a solid (0.09 g, 52%) mp 202-204 °C, $[\alpha]_D$ +6.6 (c0.3, MeOH); ir(Nujol): 3440m,sh and 3320w,br (NH and NH_2), 1690w,br (CO ketone and COester), 1625m,sh (C=C) cm^{-1}; ^{1}H nmr (dimethyl-d6 sulfoxide) see Table 4; ^{13}C nmr (dimethyl-d6 sulfoxide) see Table 5; ms: m/z 243 (15.23), 216 (31.51), 188 (74.79), 91(100), 43(14.50).

2-Amino-3-ethoxycarbonyl-5-*iso*propylpyrrolin-4-one (**15**).

According to the previous procedure the title compound was obtained as a solid (0.3 g, 59%) mp 174-176 °C, $[\alpha]_D$ +8 (c0.2, MeOH); ir(Nujol): 3480s,sh, 3270s,sh and 3140m,br (NH and NH_2), 1685s,sh (CO ketone), 1655s,sh (CO ester), and 1615m,sh

(C=C) cm^{-1}; ^1H nmr (dimethyl-d6 sulfoxide) see Table 4; ^{13}C nmr (dimethyl-d6 sulfoxide) see Table 5; ms: m/z 197 (0.29), 170 (88.75), 167 (23.91), 151 (20.94), 124 (100), 43(8.01).

2-Amino-3-ethoxycarbonyl-5-*iso*butylpyrrolin-4-one (**16**).

According to the previous procedure the title compound was obtained as a solid (0.2 g, 78%) mp 180-185 °C, $[\alpha]_D$ +2.6 (c0.5, MeOH); ir(Nujol): 3480s,sh, 3260m,sh and 3140m,br (NH and NH_2), 1700m,sh (CO ketone), 1655m,sh (CO ester), and 1615m,sh (C=C) cm^{-1}; ^1H nmr (dimethyl-d_6 sulfoxide) see Table 4; ^{13}C nmr (dimethyl-d_6 sulfoxide) see Table 5; ms: m/z 212 (1.02), 181 (15.09), 170 (100), 124 (96.23), 44 (26.89).

Ackowledgments.

We thank the Committee of Research of the National Technical University of Athens, Greece, for a doctoral assistantship (M.P.)

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