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PYRROLE DERIVATIVES FROM α-KETOALDEHYDES

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ABSTRACT: The reaction between enamines from β-ketoesters or β–ketonitriles and α-ketoaldehydes was investigated. Besides simple pyrrole and pyrrolinone derivatives, some compounds containing two units of ketoaldehyde were obtained. The structures of the reaction products were established by spectral methods, mainly through the use of two-dimensional NMR techniques and heteronuclear NOE-difference experiments.

INTRODUCTION

Pyrrole derivatives may be prepared from enamines through the procedures of Hantzsch [1,2] and Feist [3,4], involving the reaction with α-haloketones and α-hydroxyketones, respectively. Nevertheless, no references to the use of α-dicarbonyl compounds for the synthesis of this kind of substances have been found in the literature. In the present report we describe the study of the reactions between enamines prepared from ß-ketoesters or β-ketonitriles and α-ketoaldehydes, which yielded some pyrrole derivatives of types depending on the structures of the starting products.

METHODS AND RESULTS

The enamines used were mainly β-aminocrotonic alkyl esters and also β-aminocrotononitrile. The ketoaldehydes were phenylglyoxal, pyruvic aldehyde and glyoxal. Attempts to use diacetyl as the dicarbonyl reagent were unsuccessful for obtaining isolatable products.

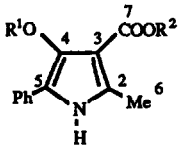
The reaction between phenylglyoxal and methyl β-aminocrotonate in methanol under refluxing conditions afforded, in 62% yield, a crystalline substance of m.p 173-175°C and molecular formula $C_{13}H_{13}NO_3$, corresponding to the condensation of a molecule of ketoaldehyde and another of enamine with removal of a water molecule. Study of its spectroscopic properties allowed us to propose for this compound structure **1** in view of the following facts:

a) In the ^1H and ^{13}C NMR spectra (see experimental part and Table I) it was possible to identify signals corresponding to the enamine fragment, which varied very little with respect to those of the methyl β-aminocrotonate used as the starting material. Likewise, the IR spectrum showed bands of β-unsaturated ester (1660 cm^{-1}) and another of NH and OH groups (3340 cm^{-1}) that decrease in intensity, but do not disappear in the acetate **2**.

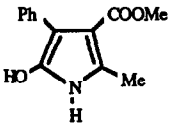
b) The remaining signals of the ^{1}H and ^{13}C NMR spectra are consistent with the presence of a phenyl group and a totally substituted ethylene group.

c) To rule out the alternative structural proposal **1a**, several heteronuclear NOE experiments (Fig 1) were carried out [5]. Thus, saturation of the signal corresponding to the hydrogen atom bonded to the nitrogen, which absorbs at 10.0 ppm, produced NOE on the adjacent non-protonated carbons (132.06 and 110.68 ppm) and negative NOE on the signal assigned to carbon atoms 2 and 6 of the phenyl group (122.81 ppm). This result unequivocally establishes position 5 for the phenyl. Furthermore, irradiation of the hydroxyl hydrogen produced NOE on the carbon atom supporting it (143.09 ppm) on the carboxyl carbon (166.91 ppm) and also on carbon atoms 2 and 6 of the phenyl group . With these experiments, apart from definitively establishing the structure of substance **1**, it was possible to unequivocally assign all the signals of the ^{13}C NMR spectrum of the compound. Substance **1** has been synthesized by TARZIA *et al.* [6] by cyclization of the enamine methyl 3-(α-methoxycarbonylbenzylamino) crotonate in basic medium.

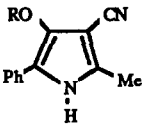
The reaction of phenylglyoxal with ethyl β-aminocrotonate and β-aminocrotononitrile afforded the corresponding hydroxypyrroles **3** and **4**, in 56 and 52% yields respectively, which were converted into their acetates **5** and **6**.



1 $R^1 = H, R^2 = Me$; **3** $R^1 = H, R^2 = Et$
2 $R^1 = Ac, R^2 = Me$; **5** $R^1 = Ac, R^2 = Et$



1a



4 R = H
6 R = Ac

Fig.1. Heteronuclear $\{^{1}H\} \rightarrow {}^{13}C$ NOE-difference spectra for compound 1. A : BB decoupled spectrum
B : Irradiated at 2.45ppm (Me-2).
C : Irradiated at 10.10ppm (NH)
D : Irradiated at 8.33ppm (OH)

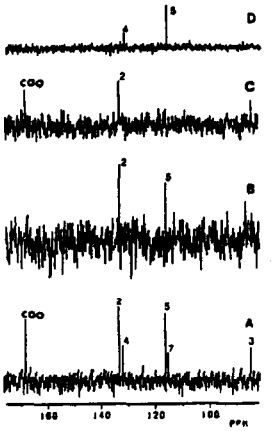
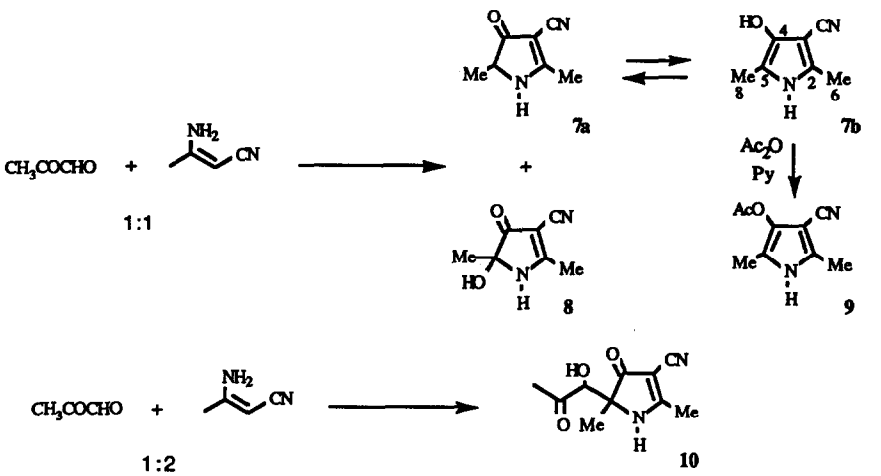


Fig.2. Heteronuclear $\{^{1}H\} \rightarrow {}^{13}C$ NOE-difference spectra for compound 9. A : BB decoupled spectrun
B : Irradiated at 9.22ppm (NH).
C : Irradiated at 2.28ppm (MeCOO) and 2.29ppm (Me-2).
D : Irradiated at 2.02ppm (Me-5).

From the product of the reaction between pyruvic aldehyde (40% in water) and β-aminocrotononitrile in equimolecular proportions , compounds **7** (13.4%), **8** (23.4%) and 1,2-propyleneglycol were isolated. Compound **7** has a m.p.= 216-218°C and a molecular formula of $C_7H_8N_2O$. Its NMR spectra in DMSO-d_6 (see experimental part and Table I) show a number of signals double that expected, pointing to the existence of an equilibrium between the keto-enolic tautomers **7a** and **7b** at an approximate ratio of 1:1. As expected, acetylation led qualitatively to a single product **9**. The location of the oxygenated function at position 4 of the pyrrolic ring was deduced from the absorption in the UV spectrum with a maximum at 230 nm, from the presence in the IR spectrum of an intense band at 1650 cm^{-1}, and from the absorption in the ^{13}C NMR spectrum at 197.13 ppm. This structure was confirmed experimentally by the generation of some NOEs. Working on the acetate **9**, which is a single species and is soluble in $CDCl_3$, we studied the heteronuclear effects produced by irradiation of the NH proton and of the protons of the methyl groups. This permitted us to confirm the structure proposed for these substances and also to assign correctly all the signals of the ^1H and ^{13}C spectra. Thus, irradiation of the NH proton affected the two carbons C_2 and C_5 adjacent to this group (133.87 and 116.62 ppm, respectively). Irradiation of the methyl absorbing at 2.02 ppm produced NOE on carbon atoms C_4 and C_5 (132.44 and 116.62 ppm) and simultaneous irradiation of the methyl groups at position 2 and of the acetate produced NOEs on C_2, C_3 (85.75 ppm) and the carboxyl carbon (169.21ppm) (fig 2).



The structure of **8** was established by comparison of its spectroscopic data with those of **7a**. Thus, the presence of the carbonyl group at C_4 was deduced from the signal at 196.08 ppm in the ^{13}C spectrum and from the intense band in the IR spectrum at 1660 cm^{-1}. The presence of the OH group at C_5 was deduced from the chemical shift (78.23 ppm) observed for this carbon; from the existence of a methyl singlet at 1.29 ppm in the ^1H spectrum, and from the observation of two signals of exchangeable protons, one corresponding to the NH group at 10.14 ppm and the other to the tertiary OH group at 6.72 ppm, whose shift agrees with its bonding towards the carbonyl group at position 4.

When this reaction was performed using the ratio 1:2 between the enamine and the aldehyde, after chromatography on silica gel, a crystalline substance (m.p 181-183°C) was isolated in 32% yield.In its MS it

showed M^+ at m/z=208 corresponding to a molecular formula $C_{10}H_{12}N_2O_3$, which indicated that this substance must have resulted from the condensation of one molecule of enamine with two molecules of pyruvic aldehyde. Its NMR spectra (see experimental part and Table I) were in agreement with this observation; apart from signals belonging to the enamine fragment the following groupings were observed: a methyl ketone (1720 cm^{-1} in the IR; 2.10 ppm 3H,s in ^1H; 27.02 *CH*$_3$ and 208.17 ppm *CO* in ^{13}C NMR spectra) ; an isolated secondary carbinol group (3.97 ppm 1H,d,J=5.9Hz, *CH* and 6.35 ppm 1H, d, J=5.9 Hz, *OH* in ^1H; 79.01 ppm, *CH* in ^{13}C); a methyl on a tetrasubstituted carbon atom (1.22 ppm 3H,s in ^1H and 19.64 ppm in ^{13}C), and a non-protonated sp^2 carbon at 196.36 ppm in ^{13}C that must correspond to a carbonyl group at position C_4 (1665 cm^{-1} in IR) by comparison with data from **7a** and **8**. With these data structure **10** is proposed for this substance. As in the previous reaction, propyleneglycol was also formed as by-product.

The reaction between pyruvic aldehyde and methyl β-aminocrotonate at a proportion of 1:1 under refluxing conditions in MeOH afforded substance **11** in 40% yield; the spectral data of this substance are in agreement with those of **8**, the major difference being the shift of the C_3 signal in their ^{13}C NMR spectra, although this is in accordance with the different effect of the CN and COOMe groups on the attached carbon atom. Confirmation of this structure was obtained from the observation of heteronuclear NOEs originated by irradiation of the NH and OH protons and of the methyl groups on C_2 and C_5 (Fig. 3).

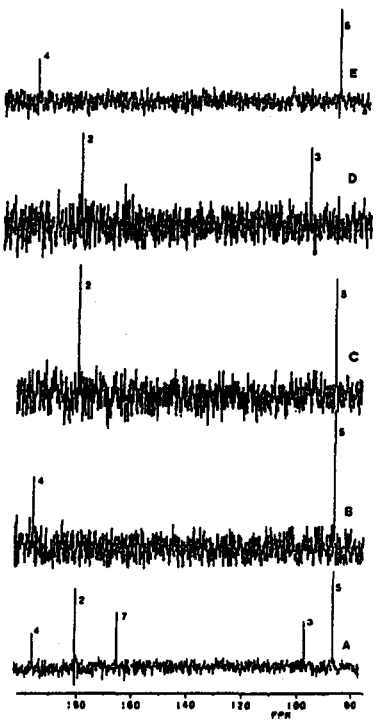


Fig. 3- Heteronuclear $\{^1H\} \rightarrow {}^{13}C$ NOE difference spectra for compound **11**.
A : BB decoupled spectrum. B : Irradiated at 6.35ppm (OH).
C : Irradiated at 9.73ppm (NH). D : Irradiated at 2.38ppm (Me-2).
D : Irradiated at 1.20ppm (Me-5).

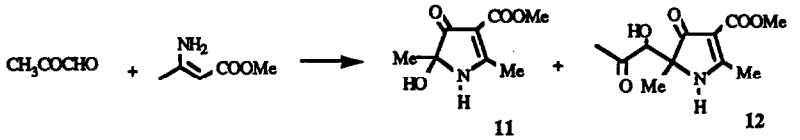
Table I. ^{13}C-NMR (50.3MHz) data for Compounds 1-3, 5-11, and 14-16

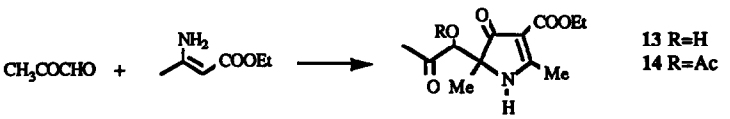
C No.	1	2*	3	5	6	7a	7b	8	9*	10	11	14*	15	16
2	132.06	134.45	131.80	134.01	135.90	178.84	130.80	178.65	133.87	178.47	179.55	180.50	153.59	134.35
3	100.53	105.66	100.54	104.85	87.27	82.99	81.58	88.75	85.75	82.00	95.99	100.47	101.72	108.52
4	143.09	129.96	143.05	130.12	129.78	197.13	139.14	196.08	132.44	196.36	195.13	195.30	36.69	94.71
5	110.68	119.51	110.53	118.51	119.66	60.83	116.73	78.23	116.62	70.69	85.39	67.68	173.36	129.42
6	13.13	13.74	13.10	13.09	12.27	15.48	11.94	15.38	12.25	14.90	16.90	17.09	12.81	12.06
7	166.91	170.46	166.51	168.98	114.63	109.04	115.40	115.34	115.17	115.28	164.11	163.64	163.79	167.78
8	---	---	---	---	---	15.17	8.94	22.25	9.32	19.64	22.52	19.63	---	---
others														
	Ph	**Ph**	**Ph**	**Ph**	**Ph**					**C5-chain**		**C5-chain**		
1'	123.96	126.60	123.93	126.07	127.09					79.01		79.81		
2',6'	122.81	126.60	122.71	124.30	124.95					208.17		202.19		
3',5'	128.30	128.74	128.26	128.57	129.13					27.02		27.75		
4'	131.93	132.98	131.89	132.52	132.90									
	OMe	**OMe**	**OEt**	**OEt**						**OMe**	**OMe**	**OMe**		
	50.49	50.67	59.14	58.53						49.85	50.23	50.07		
			14.15	14.08										
		OAc		**OAc**	**OAc**				**OAc**			**OAc**		**OAc**
		164.37		163.01	168.84				169.21			169.70		164.75
		20.83		20.44	20.48				20.31			20.05		20.03

δ values in ppm from TMS as internal standard. Solvent DMSO-d_6. (*) $CDCl_3$.

In this reaction, propyleneglycol was also formed and the presence of another compound in a very small amount was detected, although it was not possible to isolate it in pure form; however, structure **12**, similar to that of **10**, can be proposed. The reaction between these compound was repeated varying the proportion to 1:2 (enamine / aldehyde), but failed to produce an increase in the proportion of **12** in the reaction product, althought a 64% yield in **11** was achieved.

Finally, the reaction between pyruvic aldehyde and ethyl β-aminocrotonate at a ratio of 1:1 in refluxing ethanol yielded a substance (42%) of m.p.= 171-173°C and molecular formula $C_{12}H_{17}NO_5$, for which the structure **13** was proposed by comparison with substance **10**. Using a molar ratio 1:2 for the reagents, the same compound was isolated in 48% yield. The reaction was studied varying temperature, noting that it developed in the same way even at room temperature. Treatment of **13** with acetic anhydride under standard conditions afforded the monoacetate **14**.





Confirmation of the structures proposed for **10**, **12** and **13** was carried out on substance **13** by direct and indirect H/C heteronuclear correlations (Table II) and by heteronuclear NOE experiment , as shown in fig 4.

Table II. Direct and long-range $^1H/^{13}C$ NMR correlations* for compound **13** #

C No	δppm	Attached H,δ ppm	long-range connected H
2	179.17		6
3	99.63		6,NH (9.65ppm)
4	195.27		11,NH
5	69.51		8,11,NH
6	16.64	2.49*s*	
7	163.41		12
8	79.13	3.92*d*	11,OH*d* (6.06ppm)
9	208.10		8,10,OH
10	27.13	2.05*s*	
11	19.69	1.16*s*	
12	57.90	4.03*q*	13
13	14.34	1.17*t*	12

*Operating conditions are described in the experimental part.
#Numbering used is that shown in fig.4

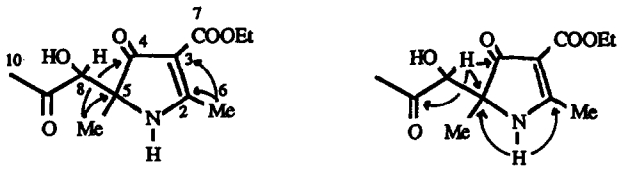
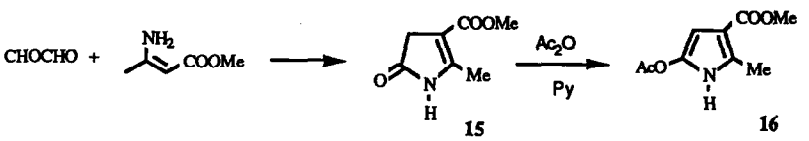


Fig. 4 Heteronuclear $\{^1H\}\rightarrow {}^{13}C$ NOEs observed for compound **13**

Under similar reaction conditions the condensation of glyoxal (40% in water) with methyl ß-aminocrotonate was performed, isolating, after chromatography and crystallization in 29% yield, an orange substance with m.p.= 198-200°C and a molecular formula $C_7H_9NO_3$. The structure **15** has been assigned to this substance in view of its spectroscopic data which reveal the existence of an amide carbonyl group that appears at 173.36 ppm in the ^{13}C NMR spectrum and that gives a band in the IR spectrum at 1730 cm^{-1} and of an isolated methylene group absorbing at 36.69 ppm in the ^{13}C spectrum and at 3.13 ppm in the ^1H spectrum and showing homoallylic coupling (J=2.3Hz) with protons of the methyl at C_2.

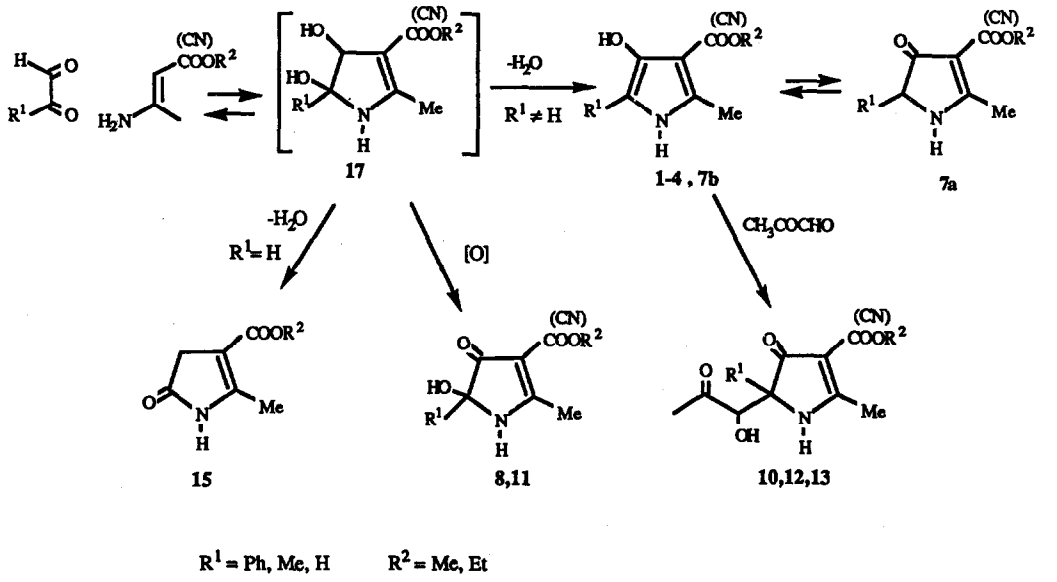
For additional proof of the structure of substance **15**, heteronuclear NOE experiments were performed by selective irradiation of the NH and methylene protons. In the first case, an increase was observed in the intensity of the signals of the carbonyl and of the olefinic C_2 (173.36 and 153.59 ppm, respectively). In the second case these increases were observed on the carbonyl itself and on C_5 (101.72 ppm). When **15** was treated with acetic anhydride in pyridine it was converted into its tautomeric acetate **16**.



DISCUSSION

The overall proposal of the reaction mechanism between enamines and α-ketoaldehydes that serves to explain the formation of all the products obtained under the different circumstances examined is shown in the scheme 1.

The reaction presumably involves nucleophilic addition of the enamine to the aldehyde group to form the potential C_3-C_4 bond of the pyrrole, followed by regeneration of the enamine and addition of the amino group to the ketone. Loss of water from the intermediate cyclic diol of type **17** produced, occurs to give the hydroxypyrroles of type **1-4, 7b** or the tautomeric ketone of type **7a** when there is an aryl or alkyl substituent at C_5, respectively. However, if there is no alkyl or aryl substituent at C_5, then pyrrolidones of type **15** are formed. The formation of hydroxylpyrrolinones of type **8** and **11** may be accounted for by oxidation by pyruvic aldehyde, and this was confirmed by the fact that reaction also occurred under nitrogen, and by the simultaneous formation of 1,2-propylene glycol. Pyruvic acid was not involved as its reaction with the enamine afforded an intractable product which did not exhibit any NMR signals corresponding to those observed for the pyrrolinones **8** or **11**. Formation of the products **10, 12** and **13** can be accounted for by an aldol type reaction of a second mole of pyruvic aldehyde with the initial cyclic enol, or ketone.



SCHEME 1

As confirmation of this proposal it should be noted that the pyrrolinone **7a** in the presence of pyruvic aldehyde was converted into **10**. It should also be noted that although the reaction conditions employed in all cases consisted in heating under reflux (MeOH or EtOH), it appears that the transformation can occur in a similar fashion at room temperature, as was observed in the case of **13**.

EXPERIMENTAL.-

General experimental procedures. Mps were determined in capillaries on a Buchi 510 instrument and are uncorrected. UV spectra were recorded in EtOH on a Hitachi 100-60 spectrometer. IR spectra were obtained in KBr disks on a Beckman Acculab VIII spectrophotometer. Unless otherwise stated ^{1}H NMR (200,13 MHz) and ^{13}C NMR (50.3 MHz) spectra were measured in DMSO-d_6 with TMS as internal standard on a Bruker WP 200 SY. δ values are expressed in ppm. EIMS (70 ev) run on a VG-TS-250 mass spectrometer.

Methyl 4-hydroxy-2-methyl-5-phenylpyrrolyl-3-carboxylate (1). A solution of methyl β-aminocrotonate (4.53g, 39.4 mmol) and phenylglyoxal hydrate (6g, 39.4 mmol) in MeOH (45ml) was refluxed for 6h. The solvent was partially removed and the solid precipitate filtered and recrystallized from MeOH to give **1** (5.6g, 62%). M.p. 173-175°C. IR: 3340, 1660, 1605, 1500, 1430,1370, 1250, 1110, 1000, 970 cm^{-1}. ^{1}H NMR δ: 2.45 (3H,*s*), 3.79 (3H,*s*), 7.1-7.8 (5H,*m*), 8.33 (1H,*s*), 10.10 (1H,*s*). UV λmax: 292 , 239 and 205 nm (ε =12.036, 10.062 and 9.150). MS *m/z* 231(47,M$^+$), 199 (100), 128 (10), 104 (38), 67 (18). Anal.calc.for $C_{13}H_{13}NO_3$:C 67.56, H 5.63, N 6.06%, found: C 67.65, H 5.67, N 5.93%.

Acetylation of 1. 1.0 g of **1** in anhydrous pyridine (3ml) was allowed to react with acetic anhydride (3ml) at room temperature.After the usual work-up it afforded **2** (1.0g). mp.158-160°C (CH_2Cl_2). IR: 3320,

1750, 1690, 1615, 1490, 1450, 1370, 1270, 1230, 1110, 970 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.26 (3H,*s*), 2.34 (3H,*s*), 3.75 (3H,*s*), 7.1-7.4 (5H,*m*), 8.90 (1H,*s*). MS *m/z* 273 (8,M^+), 231 (41), 199 (100), 128 (8), 104 (21).

Ethyl 4-hydroxy-2-methyl-5-phenylpyrrolyl-3-carboxylate (3). Compound **3** was prepared similarly (refluxed in EtOH) to **1**. 5.4 g (56%) were obtained from 6 g of phenylglyoxal hydrate. Recrystallized from EtOH, m.p. 159-161°C. IR: 3340, 1660, 1600, 1500,1450, 1380, 1250, 1170, 1115, 1020 cm^{-1}. ^1H NMR δ: 1.29(3H,*t* J=7.1Hz), 2.42 (3H,*s*) , 4.26 (2H,*q* J=7.1Hz), 7.0-7.7 (5H,*m*), 8.29 (1H,*s*). UV λmax : 292, 237 and 206 nm (ε =15.460, 13.190 and 12.150)

Acetylation of 3 .Treatment of **3** with Ac_2O-C_5H_5N in the usual way afforded **5**. M.p. 182-184°C (EtOH). IR:3350, 1750, 1690, 1615, 1490, 1450, 1270, 1225, 1100, 1020 cm^{-1}. ^1H NMR δ:1.23 (3H,*t* J=7.2 Hz), 2.26 (3H,*s*), 2.46 (3H,*s*) , 4.13 (2H,*q* J=7.2 Hz), 7.1-7.6 (5H,*m*).

4-hydroxy-2-methyl-5-phenylpyrrolyl-3-carbonitrile (4). This was prepared similarly to **1**, 4.05 g (52%) were obtained from 6 g of phenylglyoxal hydrate. Recrystallized from isopropanol , m.p. 273-275°C. IR: 3310, 2205, 1655, 1530, 1300, 1090 cm^{-1}. ^1H NMR δ: 2.20 (3H,*s*) , 7.3-7.7 (5H,*m*). UV λmax: 305, 230 and 204 nm (ε =6.400, 5.740 and 2.030).

Acetylation of 4. Treatment of **4** with Ac_2O-C_5H_5N in the usual way afforded **6** ,m.p. 175-177°C (ether). IR: 3360, 2205, 1750, 1605, 1500, 1430, 1375, 1215, 1200, 1050, 1030 cm^{-1}. ^1H NMR δ: 2.35 (3H,*s*), 2.38 (3H,*s*), 7.2-7.6 (5H,*m*). UV λmax: 275 and 218 nm (ε = 14.880 and 16.200). Anal.Calc.for $C_{14}H_{12}N_2O_2$: C, 69.98, H 4.99, N 11.66%, found: C 70.03, H 5.01, N 11.59 %.

Reaction of pyruvic aldehyde with β- aminocrotononitrile: Preparation of 7, 8 and 10 .

a) A mixture of β -aminocrotononitrile (4.6g) and pyruvic aldehyde (40% in water, 10.6 ml) (molar ratio 1:1) in MeOH (30 ml) was refluxed for 10 h. The solvent was removed and **8** was obtained by crystallization. After evaporation of solvent the mother liquors were chromatographed over silica gel (100g) and by elution with Hexane-EtOAc-MeOH (1:0.9:0.1) **7** 1.0g (13.4%) , **8** 1.9g (23.4%) and propyleneglycol were isolated.

7 M.p. 216-218°C (MeOH). IR: 3170, 3080, 2200, 1650, 1520, 1340, 1220, 1005 cm^{-1}.UV λmax: 290 and 230 nm (ε =7.380 and 7.023). Anal. calc. for $C_7H_8N_2O$: C 61.75, H 5.93, N 20.57%, found : C 61.53, H 6.25, N 19.87%. **7a** ^1H NMR δ: 1.19 (3H,*d* J=7.3 Hz), 2.27 (1H,*d* J=1.5 Hz), 3.93 (1H,*dq* J_1=7.3 J_2=1.5 Hz), 10.60 (1H,*s*). **7b** ^1H NMR δ: 1.95 (3H,*s*), 2.15 (3H,*s*), 8.10 (1H,*s*), 9.78 (1H,*s*).

8 M.p. 146-148°C (MeOH) . IR: 3270, 3190, 2205, 1660, 1560, 1530, 1320, 1180 cm^{-1}. ^1H NMR δ: 1.29 (3H,*s*), 2.31 (3H,*s*), 6.72 (1H,*s*) 10.14 (1H,*s*). UV λmax : 312, 227 and 210 nm (ε = 7.390, 11.740 and 10.177). MS *m/z* 152 (49,M^+) , 135 (34), 109 (36), 96 (31), 82 (100).

b) β-aminocrotononitrile (4.6g) and pyruvic aldehyde (40% in water, 21.2 ml) (molar ratio1:2), in MeOH (30 ml) were refluxed for 7 h. The solvent was removed and the product was purified by chromatography over silica gel (100g) with EtOAc-MeOH (9:1) giving 2.44g (32%) of **10** . M.p. 181-183°C (EtOAc/Hexane). IR : 3250, 3160, 2200, 1720, 1665, 1540, 1300, 1090 cm^{-1}. ^1H NMR δ: 1.22 (3H,*s*), 2.10 (3H,*s*), 2.24 (3H,*s*), 3.97 (1H,*d* J=5.9 Hz), 6.35 (1H,*d* J=5.9 Hz), 9.94 (1H,*s*). UV λmax: 299 and 226 nm (ε= 5.677 and 7.812). MS *m/z* 208 (41,M^+), 165 (25), 149 (31) , 136 (100).

Acetylation of 7 . Treatment of **7** with Ac_2O-C_5H_5N in the usual way afforded **9**. IR: 3220, 2200, 1760, 1630, 1420, 1360, 1190, 1005 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 2.02 (3H,*s*), 2.28 (3H,*s*), 2.29 (3H,*s*), 9.22 (1H,*s*)

Methyl 5-hydroxy-2,5-dimethyl-4-oxo-2-pyrrolin-3-carboxylate (11)

a) A solution of methyl β -aminocrotonate (7.56g) and pyruvic aldehyde (40% in water, 12.5 ml) (molar ratio 1:1) in MeOH (20 ml) was refluxed for 4 h. The solvent was removed and the residue was purified by chromatography on silica gel (EtOAc/ether/MeOH 3:1:1) and crystallization to give **11** (5g, 40%). M.p. 216-

218°C (MeOH).IR : 3380, 3180, 1670, 1590, 1520, 1390, 1330, 1210, 1080, 1010 cm^{-1}. ^1H NMR δ: 1.20(3H,*s*), 2.38(3H,*s*), 3.55(3H,*s*), 6.35(1H,*s*), 9.73 (1H,*s*). UV λmax: 290 and 239 nm (ε = 4.660 and 6.700) . Anal.calc. for $C_8H_{11}NO_4$: C 51.89, H 5.95, N 7.56%, found: C 52.17, H 6.06, N 7.30 %.

b) Under the same conditions, but with a molar ratio 1:2 of reactives, **11** was isolated in 64% yield.

Ethyl 5-(1-hydroxy-2-oxopropyl)-2,5-dimethyl-4-oxo-2-pyrrolin-3-carboxylate (13). A mixture of ethyl β-aminocrotonate (7.2g) and pyruvic aldehyde (40% in water, 10.6 ml) in EtOH (20 ml) was refluxed for 8h. The solvent was removed and the residue was purified by chromatography over silica gel (EtOAc/ether/MeOH 3:1:1) and crystallization to give 5.7g (42%) of **13** . M.p. 171-173°C (EtOH). IR: 3380, 3240, 1710, 1690, 1630, 1540, 1510, 1330, 1130, 1080, 1030 cm^{-1}. ^1H NMR (see Table II). UV λmax: 292 and 247 nm (ε =10.020 and 13.274). MS *m/z* 255 (3,M^+), 183 (20), 137 (100). Anal.calc. for $C_{12}H_{17}NO_5$: C 56.49, H 6.72, N 5.49 %, found: C 56.05, H 6.81, N 5.33 %.

Acetylation of 13 . Acetylation under the usual conditions gave **14**. IR: 3400, 1740, 1715, 1670, 1535, 1500, 1360, 1220, 1070, 1050, 1010 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 1.32 (3H,*t* J=7.1Hz), 1.41 (3H,*s*), 2.14 (3H,*s*), 2.16 (3H,*s*), 2.54 (3H,*s*), 4.23 (2H,*q* J=7.1Hz), 5.16 (1H,*s*), 9.14 (1H,*s*).

Methyl 2-methyl-5-oxo-2-pyrrolyl-3-carboxylate (15). Methyl β-aminocrotonate (17.6 g) and glyoxal (40 % in water, 17.5ml) (molar ratio 1:1) in MeOH (40 ml) were refluxed for 7 h. The solvent was removed, and the residue purified by crystallization from MeOH , to yield 6.9 g (29%) of **15**. M.p. 198-200ºC. IR: 3110, 1730, 1700, 1640, 1470, 1360, 1210, 1075 cm^{-1}. ^1H NMR δ: 2.22 (3H,*t* J=2.3Hz), 3.13 (2H, *q* J=2.3Hz), 3.60 (3H,*s*), 8.74 (1H,*brs*). UV λmax: 279 and 218 nm (ε =11.783 and 5.000). Anal. calc. for $C_7 H_9 NO_3$: C 54.19, H 5.8, N, 9.03 % , found: C 54. 53, H 5.63, N 8.82 %.

Acetylation of 15. Acetylation under the usual conditions gave **16**. M.p. 143-145ºC (MeOH).IR: 3280, 1770, 1680, 1590, 1530, 1430, 1225, 1200, 1090, 1030 cm^{-1}. ^1H NMR δ : 2.23 (3H,*s*), 2.36 (3H,*s*), 3.67 (3H,*s*), 5.91 (1H,*s*), 7.60 (1H,*s*). UV λmax: 256 and 220 nm (ε =7.620 and 11.447).

Heteronuclear NOE-difference experiments . They were performed using an automation program with slight modifications to that described in ref. 5. The selected proton(s) was (were) irradiated for a minimun of 5 sec to generate heteronuclear NOE before recovering a NOE-FID in the BB decoupling mode. Another FID (BB) without NOE was then obtained after off-resonance irradiation in the ^1H region near (50-60 Hz apart) the absorption of the proton(s) considered. After subtracting both FIDs, repeating the experiment for an adequate signal / noise ratio and Fourier transforming the spectra shown in fig. 1,2 and 3 were obtained.

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