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REACTION OF ACYLPYRUVIC ACID ESTERS WITH HYDRAZIDES

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Hydrazides reacted with acylpyruvic acid esters possessing a terminal straight chain alkyl substituent at the C=O bond distal from the ester group, giving 5-hydroxy-2-pyrazolines. Acylpyruvates with bulky terminal substituents underwent condensation at the C=O bond adjacent to the ester group, giving products with hydrazone or 5-hydroxy-2-pyrazoline structure and capable of displaying ring-chain equilibrium between these tautomers in solution.

Keywords: acylpyruvic acid ester hydrazones, benzoylhydrazine, picolinic acid hydrazide, 5-hydroxy-2-pyrazolines, ring-chain tautomerism.

The reaction of hydrazides with aroylpyruvic acid esters with the general formula $MeO_2CCOCH_2COC_6H_4X$ proceeded with 100% regioselectivity at the C=O bond adjacent to the ester group, regardless of the electronic properties of aromatic ring substituent [1-3]. In the crystalline state, the resultant derivatives had either hydrazone or 5-hydroxy-2-pyrazoline structure, while forming tautomeric mixtures of these forms in solution [3, 4].

In the present work, we studied the reaction of aliphatic acylpyruvic acid esters $RO_2CCOCH_2COR^1$ **1a-f** with hydrazides **2a-c**. We were interested in the terminal alkyl substituent role in determining the regioselectivity of the reaction with hydrazides and tautomeric transformations in the products of these reactions.

Benzoylhydrazine **2b** was used as the main nucleophilic reagent. The reaction was carried out under mild conditions, by mixing equimolar amounts of the reagents in ethanol or methanol and maintaining until the end of the reaction without using any acidic catalysts. At the end of the reaction as indicated by thin-layer chromatography, the solvent was removed at reduced pressure, and the residue was analyzed using ^1H or ^{13}C NMR spectroscopy. In interpreting these spectral data, we should first take into account that the reaction could proceed through two pathways, while the condensation products, independently of which C=O bond reacted, could exist in several tautomeric forms similar to nitrogen derivatives of other 1,3-dicarbonyl compounds [4].

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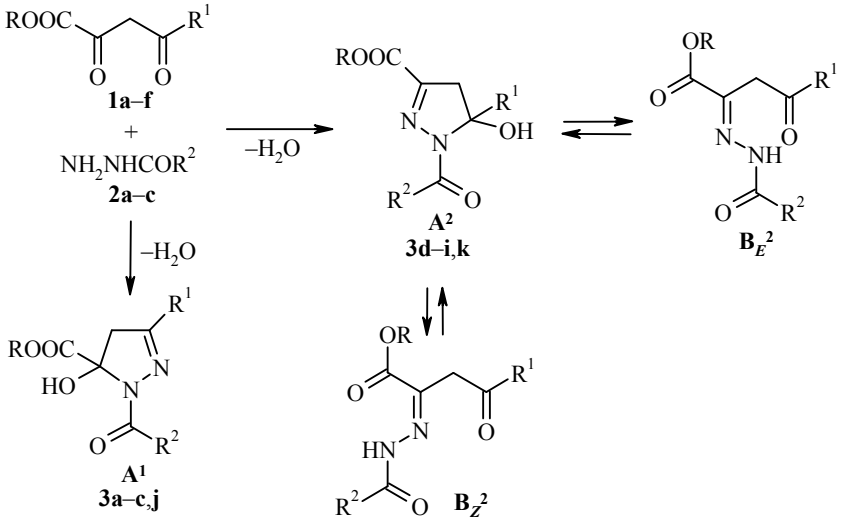
Let us examine the particular example of 2,4-dioxopentanoic acid methyl ester **1a** reaction with benzoylhydrazine (**2b**). The crystalline material obtained at the reaction completion (compound **3a**) exhibited a single set of ^{1}H NMR signals in chloroform solution. This finding primarily indicates that the reaction was 100% regioselective at one of the C=O bonds.



1, **3 a-c** R = Me, **1d-f**, **3d-k** R = Et; **1a**, **3a** R^1 = Me, **1b**, **3b** R^1 = Et, **1c**, **3c** R^1 = Pr, **1d**, **3d**,**g** R^1 = *i*-Pr, **1e**, **3e**,**h** R^1 = *s*-Bu, **1f**, **3f**,**i-k** R^1 = *t*-Bu; **2a**, **3j**,**k** R^2 = H, **2b**, **3a-f** R^2 = Ph, **2c**, **3g-i** R^2 = 2-Py

The presence of two asymmetric doublets at 3.01 and 3.25 ppm, forming a typical AB system (J_{AB} = 18.6 Hz) indicated cyclic 5-hydroxy-2-pyrazoline structure **A^1** or **A^2** having a chiral carbon atom C-5 in the ring. This accounted for the diastereotopic nature of the methylene protons at the carbon atom C-4, leading to the appearance of an AB system in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum corresponded to the cyclic structure of this condensation product. The presence of a signal at 89.7 ppm, which should be assigned to the quaternary carbon atom C-5 of the pyrazoline ring, was the most characteristic. The selection between structures **A^1** and **A^2** could be based on the IR spectral data. The ester C=O stretching band was found at 1764 cm^{-1} in the IR spectrum for product **3a** taken in a KBr pellet. This value corresponded to structure **A^1**, in which the close-lying C(5)–O and C(5)–N bonds should shift the ester C=O stretching band towards shorter wavelengths in comparison with the ordinary position of this band in the spectra of acid esters (1735-1750 cm^{-1}) [5].

Thus, the reaction of acylpyruvate **1a** with benzoylhydrazine (**2b**) occurred entirely at the distal C=O bond, and condensation product **3a** had the 5-hydroxy-2-pyrazoline structure **A^1**.

Solutions of product **3a** did not exhibit any changes in their ^{1}H and ^{13}C NMR spectra with time, and there were no new sets of resonance signals observed. This finding indicated a lack of tautomeric transformations between the cyclic structure and linear species, thus a clear preference for the 5-hydroxy-2-pyrazoline form **A^1**.

Lengthening the chain of the terminal substituent (going to acylpyruvates **1b**,**c**) did not alter the regioselectivity of the reactions with benzoylhydrazine (**2b**). Only products of condensation at the C=O bond adjacent to the alkyl group were formed. Derivatives **3b**,**c** also had the 5-hydroxy-2-pyrazoline structure **A^1**, which was entirely conserved in $CDCl_3$ solutions.

We also note that the products **3a-c** did not undergo tautomeric transformations in DMSO-d_6, which is a dipolar basic solvent.

The regiodirection of the reaction with benzoylhydrazine (**2b**) changed when bulky branched substituents were present in the acylpyruvates. The reaction of acylpyruvates **1d-f** with benzoylhydrazine (**2b**) gave only products from condensation at the C=O bond adjacent to the ester group (compounds **3d-f**). Thus, the solution phase ^{1}H and ^{13}C NMR spectra from the crystalline reaction product of acylpyruvate **1d** (R^1 = *i*-Pr) had a single set of signals corresponding to the 5-hydroxy-2-pyrazoline structure ($\mathbf{A^1}$ or $\mathbf{A^2}$). The ^{13}C NMR signal for the C-5 carbon atom was found at 101.1 ppm, while the quaternary carbon atom ^{13}C NMR signal for compounds **3a-c** with structure $\mathbf{A^1}$ was located in a different region (89.5-90.0 ppm). This difference indicates that the product **3d** most likely has the cyclic structure $\mathbf{A^2}$, which was confirmed by IR spectroscopy. The ester C=O stretching band in the IR spectrum of product **3d** recorded in a KBr pellet was found at 1739 cm^{-1}. We recall that the analogous band, for example, in the case of compound **3a** was found at 1764 cm^{-1}.

The ^{1}H and ^{13}C NMR spectra of product **3d** solutions did not change over time. The possible linear tautomeric structures were not favored, compared to the 5-hydroxy-2-pyrazoline form $\mathbf{A^2}$.

Thus, the presence of a relatively bulky isopropyl substituent was sufficient to completely alter the regiodirection of the acylpyruvate reaction with hydrazides. Hence, it was not surprising that the pyruvates **1e**,**f** having even bulkier *sec*-butyl and *tert*-butyl groups as the terminal substituents yielded the derivatives **3e**,**f**, which were products of condensation at the C=O bond adjacent to the ester group. However, the products **3e**,**f** deserve a separate discussion.

The ^{1}H and ^{13}C NMR spectra of derivative **3e** in $CDCl_3$ recorded immediately after dissolution corresponded to the 5-hydroxy-2-pyrazoline form $\mathbf{A^2}$, represented by two diastereomers due to two chiral centers. This was indicated by the doubling of several ^{1}H and ^{13}C NMR signals. For example, the ^{13}C NMR signals at 100.9 and 101.0 ppm corresponded to the C-5 carbon atoms of the diastereomeric heterocycles.

Partial transformation of compound **3e** into a hydrazone form, most likely with *Z*-configuration $\mathbf{B}_{\boldsymbol{Z}}^{\mathbf{2}}$ permitting the formation of an intramolecular chelate hydrogen bond, gradually occurred in solution. The NH proton and carbonyl oxygen atom of the ester group participated in the formation of this intramolecular hydrogen bond. The ^{1}H NMR singlets appearing at 3.87 and 13.52 ppm indicated the formation of a hydrazone tautomer. The signal at 3.87 ppm should be assigned to methylene group protons, while the signal at 13.52 ppm with only half the intensity of the former signal belonged to the amide NH proton. The relatively downfield position of the amide proton signal was a direct indication of a strong intramolecular chelate hydrogen bond and, thus, *Z*-configuration of the hydrazone tautomer $\mathbf{B}_{\boldsymbol{Z}}^{\mathbf{2}}$.

A peculiar ring-chain-ring equilibrium was established for compound **3e** in $CDCl_3$ solution after 3 days, featuring two 5-hydroxy-2-pyrazoline forms differing in the chiral center configurations, namely, (*RR,SS*)-$\mathbf{A^2}$ and (*RS,SR*)-$\mathbf{A^2}$, and the *Z*-hydrazone form $\mathbf{B}_{\boldsymbol{Z}}^{\mathbf{2}}$. The fraction of form $\mathbf{B}_{\boldsymbol{Z}}^{\mathbf{2}}$ was only about 5%. The ratio of the diastereomers in the tautomer $\mathbf{A^2}$ was 3:2. These diastereomers converted into each other through *E*-isomer $\mathbf{B}_{\boldsymbol{E}}^{\mathbf{2}}$ of the hydrazone form, in which the suitable structural fragments could approach, permitting reversible cyclization. This *E*-isomer was not detected by ^{1}H NMR spectroscopy but was predicted to be a necessary intermediate species in the observed equilibrium.

The hydrazone form $\mathbf{B^2}$ in DMSO-d_6 solution was not detected in the ^{1}H and ^{13}C NMR spectra of compound **3e**. Formally, we can discuss a ring-ring equilibrium of two cyclic 5-hydroxy-2-pyrazoline forms $\mathbf{A^2}$ differing in the configuration of the asymmetric centers.

Compound **3f**, which was obtained from the condensation of benzoylhydrazine (**2b**) with acylpyruvate **1f** containing a terminal *tert*-butyl group, had the hydrazone structure $\mathbf{B^2}$ in crystalline state. The IR spectrum of this compound recorded in a KBr pellet had absorption bands in the stretching region at 1706 and 1744 cm^{-1}, indicating that the crystalline product **3f** existed in the hydrazone form $\mathbf{B^2}$. The band at 1706 cm^{-1} should be assigned to a ketonic C=O stretching band, while the band at 1744 cm^{-1} should be assigned to an ester C=O stretching band. The solid phase ^{13}C NMR spectrum of product **3f** exhibited a set of resonance signals corresponding to hydrazone structure $\mathbf{B^2}$. The signal at 211.5 ppm quite likely belonged to the carbon atom of the ketonic C=O bond.

The ^{1}H NMR spectrum of compound **3f** in $CDCl_3$ recorded immediately after preparation of the solution contained two sets of resonance signals. One set was that of the cyclic form $\mathbf{A^2}$, while the other corresponded to one of the diastereomers of hydrazone form $\mathbf{B^2}$. The intensity ratio of these two sets stopped changing after a few minutes. Equilibrium was apparently very soon established between the two forms. Such a behavior would be possible if the crystalline compound **3f** had the *E*-hydrazone structure $\mathbf{B}_E^2$, in which the arrangement of the functional groups, NH bond, and ketonic C=O bond provided for reversible cyclization to give the 5-hydroxy-2-pyrazoline structure $\mathbf{A^2}$.

A third set of signals appeared after some time in the solution phase spectrum of compound **3f**, indicating formation of the hydrazone *Z*-isomer $\mathbf{B}_Z^2$. The signal for methylene group protons at 3.94 ppm and NH proton at 13.51 ppm belonged to the diastereomer formed. The downfield position of the signal at 13.51 ppm is due to a strong intramolecular hydrogen bond, as noted above, possible only for the *Z*-configuration of the hydrazone fragment in form $\mathbf{B}_Z^2$.

The appearance of the spectrum ceased to change after 72 h, and equilibrium was established between the cyclic form $\mathbf{A^2}$ and the hydrazone diastereomers $\mathbf{B}_Z^2$ and $\mathbf{B}_E^2$. The $\mathbf{B}_Z^2$ diastereomer was the main component comprising 85% of the equilibrium mixture, while the $\mathbf{B}_E^2$ diastereomer comprised 10% and the fraction of 5-hydroxy-2-pyrazoline form $\mathbf{A^2}$ was 5%.

Hence, the crystalline derivative **3f** existed as hydrazone $\mathbf{B}_E^2$ with *E*-configuration at the C=N bond. A rapid equilibration to the cyclic form $\mathbf{A^2}$ occurred in $CDCl_3$, facilitated by a favorable arrangement of the nucleophilic and electrophilic sites. The subsequent transformation to *Z*-hydrazone form $\mathbf{B}_Z^2$ was slow, since a change in the C=N bond configuration was required. The predominance of this form in the observed three-component equilibrium was caused by its greater stability due to a chelate intramolecular hydrogen bond.

When DMSO-d_6 was used as the solvent, no changes in the ring-chain equilibrium were observed, but the *E*-diastereomer $\mathbf{B}_E^2$ became dominant within the hydrazone form (68%), while the fraction of *Z*-diastereomer $\mathbf{B}_Z^2$ was 9% and the fraction of 5-hydroxy-2-pyrazoline form $\mathbf{A^2}$ was 23%. The predominance of the *E*-hydrazone diastereomer within the linear tautomer should be ascribed to its greater polarity relative to the *Z*-isomer and, thus, better solvation by the dipolar solvent. The possibility of forming strong intermolecular hydrogen bonds between the NH group of diastereomer $\mathbf{B}_E^2$ and highly basic dimethyl sulfoxide molecules may have also contributed to the stabilization of form $\mathbf{B}_E^2$.

Comparison of products **3d-f** obtained by condensation of benzoylhydrazine **2b** with acylpyruvates **1d-f** at the C=O bond adjacent to the ester group clearly revealed a strong dependence of the ring-chain equilibrium between 5-hydroxy-2-pyrazoline form $\mathbf{A^2}$ and linear hydrazone tautomer $\mathbf{B^2}$ on the bulk of the terminal substituent in the structure of the starting pyruvates. The presence of an isopropyl substituent in compound **3d** did not guarantee the appearance of the linear tautomer in solutions, while the introduction of a somewhat bulkier *sec*-butyl group (compound **3e**) was sufficient to make the hydrazone tautomer $\mathbf{B^2}$ competitive. A *tert*-butyl group in the acylpyruvate structure provided for almost complete predominance of hydrazone form $\mathbf{B^2}$ in the solution of derivative **3f**.

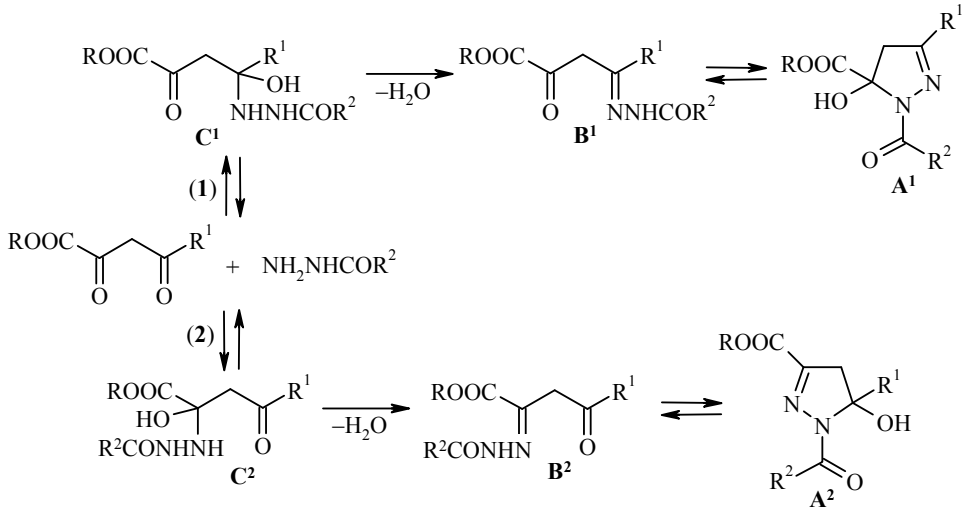
Changing the hydrazide component could also have a serious effect on tautomeric behavior of the acylpyruvate derivatives. This effect was shown in the case of products from the acylpyruvate **1d-f** condensation with picolinic acid hydrazide **2c**. As expected, the reaction led to derivatives **3g-i**, formed by condensation at the C=O bond adjacent to the ester group.

A spectroscopic study of compound **3g** showed that this acylpyruvate derivative with a terminal isopropyl group had *Z*-hydrazone structure $\mathbf{B}_Z^2$ in the crystalline state, while a ring-chain equilibrium was observed in $CDCl_3$ solution with the hydrazone diastereomers $\mathbf{B}_Z^2$ (87%) and $\mathbf{B}_E^2$ (4%), along with the 5-hydroxy-2-pyrazoline form $\mathbf{A^2}$ (9%). Derivatives **3h**,**i**, obtained by the condensation of acylpyruvates **1e** (R^1 = *s*-Bu) and **1f** (R^1 = *t*-Bu) also had the *Z*-hydrazone structure $\mathbf{B}_Z^2$ in the crystalline state, while equilibrium mixtures of the hydrazone isomers $\mathbf{B}_E^2$ and $\mathbf{B}_Z^2$ formed in $CDCl_3$. The *Z*-diastereomer with an intramolecular chelate hydrogen bond was the prevalent species (at least 95%).

Comparison of the tautomeric behavior of compounds **3d-f** (R^2 = Ph) and **3g-i** (R^2 = 2-Py) showed that in the series of products from acylpyruvate condensation with hydrazides, replacement of a phenyl ring in the hydrazide structure with a 2-pyridyl ring strongly favored the linear tautomer $\mathbf{B^2}$. This behavior may be related to stabilization of form $\mathbf{B^2}$ for the condensation products of the acylpyruvates with picolinic acid hydrazide due to an intramolecular hydrogen bond between the NH proton and the 2-pyridyl ring nitrogen atom.

The regiodirection in acylpyruvate reactions with hydrazides should be interpreted within the general framework for describing reactions of 1,3-dicarbonyl compounds with hydrazines [6-10].

Hydroxyhydrazides $\mathbf{C^1}$ and $\mathbf{C^2}$ must have initially formed in equilibrium with the starting reagents. The irreversible elimination of water from these intermediates led to the hydrazones $\mathbf{B^1}$ and $\mathbf{B^2}$, which may partially or completely convert into 5-hydroxy-2-pyrazolines $\mathbf{A^1}$ and $\mathbf{A^2}$.



The actual concentration of hydroxyhydrazide $\mathbf{C^1}$ may have been insignificant but the significantly easier irreversible elimination of water from this species enabled the predominant or even exclusive formation of condensation product at the C=O bond adjacent to the alkyl substituent. The concentration of hydroxyhydrazide $\mathbf{C^1}$ was maintained by the reversibility of the initial reaction steps. The reaction of acylpyruvates **1a-c** with benzoylhydrazine **2b** proceeded precisely in this manner. The small effective bulk of terminal *n*-alkyl groups permitted the competitive appearance of hydroxyhydrazide $\mathbf{C^1}$, opening a pathway to the formation of the corresponding final products. In this case, we may assert that the regioselectivity was determined at the second step by water elimination rate from the hydroxyhydrazides $\mathbf{C^1}$ and $\mathbf{C^2}$. Increasing the bulk of the terminal substituent in the starting acylpyruvates (compounds **1d-f**) may completely suppress formation of initial hydroxyhydrazide $\mathbf{C^1}$, such that the reaction is forced through an alternative pathway, giving condensation products at the C=O bond adjacent to the ester group.

In addition, we examined the reaction of acylpyruvate **1f** with formylhydrazine **2a**, in which a hydrogen atom served as the substituent in the hydrazide component. The solution phase ^{1}H and ^{13}C NMR spectra of completed reaction mixture had two sets of resonance signals corresponding to two 5-hydroxy-2-pyrazoline structures **3j**,**k**, formed in a 2:3 ratio.

Spectral assignment of these regioisomers was carried out by comparison with the spectra of previously examined products **3a-i**.

Decreasing the bulk of the substituent in the hydrazide component somewhat enhanced the formation of hydroxyhydrazide $\mathbf{C^1}$, originating from the initial hydrazide addition to the C=O bond adjacent to the *tert*-butyl, thus leading to regioisomeric condensation products. These regioisomers could not be isolated as pure compounds by either recrystallization or thin-layer chromatography.

This study quite clearly demonstrated the crucial influence of structural features on the regiodirection in reactions of asymmetric 1,3-dicarbonyl compounds with two different C=O bonds with nitrogen nucleophiles.

EXPERIMENTAL

The IR spectra were recorded on a PerkinElmer Spectrum FT-IR instrument in KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DX-300 spectrometer (300 and 75 MHz, respectively) in $CDCl_3$. The ^{1}H NMR spectrum of ester **3e** was also recorded in DMSO-d_6. The residual solvent signals (7.26 and 2.50 ppm for the ^{1}H nuclei and 77.0 ppm for the ^{13}C nuclei) were used as internal standard. The solid phase ^{13}C NMR spectrum was recorded on a Bruker AV-500 spectrometer (125 MHz). The elemental analysis was performed on a Hewlett-Packard 185B CHN analyzer. The melting points were determined on a Thiele apparatus. The reaction progress and purity of the products were monitored by thin-layer chromatography on Silufol UV-254 plates with chloroform as the eluent and iodine vapor for visualization.

The starting acylpyruvate **1a-f** were obtained by a reported method involving the condensation of oxalic acid esters with methyl alkyl ketones [11]. Formylhydrazine (**2a**), benzoylhydrazine (**2b**), and picolinic acid hydrazide (**2c**) were obtained from Sigma-Aldrich and were recrystallized prior to use.

Reaction of Acylpyruvic Acid Esters with Hydrazides (General Method). A solution of acylpyruvate **1a-f** (1.5 mmol) in absolute alcohol (25 ml) was mixed with a solution of hydrazide **2a-c** (1.5 mmol) in absolute alcohol (25 ml). (Methanol was used as the solvent for methyl esters **1a-c**, while ethanol was used for the ethyl esters **1d-f**). The mixture was stirred for an additional 2 h and then left at room temperature until completion of the reaction. The solvent was removed under reduced pressure. The residue was dried in vacuum and recrystallized from hexane. All the products formed colorless crystals.

Methyl 1-Benzoyl-5-hydroxy-3-methyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (3a). Yield 0.315 g (80%); mp 166-167°C. IR spectrum, ν, cm^{-1}: 1764 (CO_2Me). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.11 (3H, s, 3-CH_3); 3.01 (1H, d, J_{AB} = 18.6) and 3.25 (1H, d, J_{AB} = 18.6, 4-CH_2); 3.87 (3H, s, OCH_3); 4.99 (1H, s, OH); 7.43-7.96 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 16.3 (3-CH_3); 48.8 (4-CH_2); 54.1 (OCH_3); 89.7 (C-5); 128.2 (2C), 130.5 (2C), 132.0, 133.2 (C Ph); 155.0 (C-3); 167.1, 171.0 (<u>C</u>OPh, <u>C</u>O_2Me). Found, %: C 59.59; H 5.35; N 10.62. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54; H 5.38; N 10.68.

Methyl 1-Benzoyl-3-ethyl-5-hydroxy-4,5-dihydro-1*H*-pyrazole-5-carboxylate (3b). Yield 0.269 g (65%); mp 128-129°C. ^{1}H NMR spectrum , δ, ppm (*J*, Hz): 1.22 (3H, t, *J* = 7.3, $CH_2C\underline{H}_3$); 2.45 (2H, q, *J* = 7.3, $C\underline{H}_2CH_3$); 3.01 (1H, d, J_{AB} = 18.6) and 3.24 (1H, d, J_{AB} = 18.6, 4-CH_2); 3.87 (3H, s, OCH_3); 4.97 (1H, s, OH); 7.43-8.01 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 10.9 ($CH_2\underline{C}H_3$); 23.9 ($\underline{C}H_2CH_3$); 47.2 (4-CH_2); 54.0 (OCH_3); 89.6 (C-5); 128.1 (2C), 130.6 (2C), 132.0, 133.2 (C Ph); 159.4 (C-3); 167.1, 171.1 (<u>C</u>OPh, <u>C</u>O_2Me). Found, %: C 60.79; H 5.80; N 10.07. $C_{14}H_{16}N_2O_4$. Calculated, %: C 60.86; H 5.84; N 10.14.

Methyl 1-Benzoyl-5-hydroxy-3-propyl-4,5-dihydro-1*H*-pyrazole-5-carboxylate (3c). Yield 0.248 g (57%); mp 117-118°C. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.02 (3H, t, *J* = 7.3, $CH_2CH_2C\underline{H}_3$); 1.61-1.73 (2H, m, $CH_2C\underline{H}_2CH_3$); 2.41 (2H, t, *J* = 7.1, $C\underline{H}_2CH_2CH_3$); 3.00 (1H, d, J_{AB} = 18.5) and 3.23 (1H, d, J_{AB} = 18.5, 4-CH_2); 3.87 (3H, s, OCH_3); 4.96 (1H, s, OH); 7.43-7.99 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.1 ($CH_2CH_2\underline{C}H_3$); 20.1 ($CH_2\underline{C}H_2CH_3$); 32.4 ($\underline{C}H_2CH_2CH_3$); 47.3 (4-CH_2); 54.0 (OCH_3); 89.6 (C-5); 128.1 (2C), 130.6 (2C), 132.0, 133.2 (C Ph); 159.3 (C-3); 167.1, 171.1 (<u>C</u>OPh, <u>C</u>O_2Me). Found, %: C 62.10; H 6.32; N 9.57. $C_{15}H_{18}N_2O_4$. Calculated, %: C 62.06; H 6.25; N 9.65.

Ethyl 1-Benzoyl-5-hydroxy-5-(1-methylethyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (3d). Yield 0.386 g (85%); mp 107-108°C. IR spectrum, ν, cm^{-1}: 1739 (CO_2Et). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.92 (3H, d, *J* = 6.6) and 1.12 (3H, d, *J* = 6.6, $CH(C\underline{H}_3)_2$); 1.36 (3H, t, *J* = 7.1, $OCH_2C\underline{H}_3$); 2.97-3.06 (1H, m, $C\underline{H}Me_2$); 3.02 (1H, d, J_{AB} = 19.2) and 3.23 (1H, d, J_{AB} = 19.2, 4-CH_2); 4.34 (2H, q, *J* = 7.1, $OC\underline{H}_2CH_3$); 4.65

(1H, br. s, OH); 7.45-7.88 (5H, m, H Ph). ^{13}C NMR spectrum, δ, ppm: 14.5 (CH_3); 17.1 (CH_3); 18.4 (CH_3); 34.9 ($\underline{C}HMe_2$); 40.0 (4-CH_2); 62.4 (O$\underline{C}H_2CH_3$); 101.1 (C-5); 128.3 (2C), 130.6 (2C), 132.4, 133.6 (C Ph); 146.8 (C-3); 161.9, 170.4 ($\underline{C}$OPh, $\underline{C}O_2$Et). Found, %: C 63.10; H 6.59; N 9.17. $C_{16}H_{20}N_2O_4$. Calculated, %: C 63.14; H 6.62; N 9.20.

Ethyl 1-Benzoyl-5-hydroxy-5-(1-methylpropyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (3e). Yield 0.429 g (90%); mp 103-104°C. IR spectrum, ν, cm^{-1}: 1740 (CO_2Et). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): form $\mathbf{A^2}$ (95%): 0.88-0.92 (3H, m, CH_3); 0.98-1.02 (3H, m, CH_3); 1.34 (3H, t, *J* = 7.3, OCH$_2$C$\underline{H}_3$); 1.39-1.46 (1H, m) and 1.89-1.98 (1H, m, CH(Me)C$\underline{H}_2$Me); 2.65-2.76 (1H, m, C$\underline{H}$(Me)Et); 3.02 (1H, d, J_{AB} = 18.9) and 3.18 (1H, d, J_{AB} = 18.9, 4-CH_2); 4.33 (2H, q, *J* = 7.3, OC$\underline{H}_2$CH$_3$); 4.65 (1H, br. s, OH); 7.44-7.88 (5H, m, H Ph); form $\mathbf{B_Z^2}$ (5%): 3.87 (2H, br. s, CH_2); 13.52 (1H, br. s, NH); other signals overlap with signals of form $\mathbf{A^2}$. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm (*J*, Hz): form $\mathbf{A^2}$, diastereomer I (65%): 0.78 (3H, d, *J* = 6.5, CHC$\underline{H}_3$); 0.85-1.01 (4H, m, CHC$\underline{H}_A$C$\underline{H}_3$); 1.18-1.29 (1H, m, CHC$\underline{H}_B$CH$_3$); 1.22 (3H, t, *J* = 7.3, OCH$_2$C$\underline{H}_3$); 1.78-1.83 (1H, m, C$\underline{H}$(Me)Et); 2.75 (1H, d, J_{AB} = 18.9) and 3.23 (1H, d, J_{AB} = 18.9, 4-CH_2); 4.22 (2H, q, *J* = 7.3, OC$\underline{H}_2$CH$_3$); 6.85 (1H, br. s, OH); 7.46-7.61 (5H, m, H Ph); diastereomer II (35%): 2.77 (1H, d, J_{AB} = 18.7) and 3.21 (1H, d, J_{AB} = 18.7, 4-CH_2); 6.81 (1H, s, OH); other signals overlap with signals of diastereomer I. ^{13}C NMR spectrum, δ, ppm: diastereomer I: 12.7 (CH_3); 14.5 (CH_3); 15.1 (CH_3); 24.1 (CH$\underline{C}H_2$); 40.4 (4-CH_2); 42.1 (CH); 62.3 (O$\underline{C}H_2$CH$_3$); 100.9 (C-5); 128.3 (2C), 130.6 (2C), 132.4, 133.6 (C Ph); 146.9 (C-3); 161.9, 170.4 ($\underline{C}$OPh, $\underline{C}O_2$Et); diastereomer II: 12.3 (CH_3); 13.7 (CH_3); 15.1 (CH_3); 25.5 (CH$\underline{C}H_2$); 40.7 (4-CH_2); 41.8 (CH); 62.3 (O$\underline{C}H_2$CH$_3$); 101.0 (C-5); 128.2 (2C), 130.5 (2C), 132.0, 133.6 (C Ph); 146.9 (C-3); 161.9, 170.4 ($\underline{C}$OPh, $\underline{C}O_2$Et). Found, %: C 64.08; H 6.90; N 8.88. $C_{17}H_{22}N_2O_4$. Calculated, %: C 64.13; H 6.97; N 8.80.

Ethyl 2-[(*E*)-2-Benzoylhydrazino]-5,5-dimethyl-4-oxohexanoate (3f). Yield 0.234 g (49%); mp 154-155°C. IR spectrum, ν, cm^{-1} (form $\mathbf{B_E^2}$): 1744 (CO_2Et), 1706 (COBu-*t*). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): form $\mathbf{A^2}$ (10%): 1.11 (9H, s, C(CH$_3$)$_3$); 1.32 (3H, t, *J* = 7.3, OCH$_2$C$\underline{H}_3$); 3.14 (1H, d, J_{AB} = 18.9) and 3.44 (1H, d, J_{AB} = 18.9, 3-CH_2); 4.27 (2H, q, *J* = 7.3, OC$\underline{H}_2$CH$_3$); 6.13 (1H, s, OH); 7.44-7.85 (5H, m, H Ph); form $\mathbf{B_Z^2}$ (85%): 1.23 (9H, s, C(CH$_3$)$_3$); 1.32 (3H, t, *J* = 7.3, OCH$_2$C$\underline{H}_3$); 3.94 (2H, br. s, 3-CH_2); 4.30 (2H, q, *J* = 7.3, OC$\underline{H}_2$CH$_3$); 7.51-7.95 (5H, m, H Ph); 13.51 (1H, br. s, NH); form $\mathbf{B_E^2}$ (5%): 1.25 (9H, s, C(CH$_3$)$_3$); 1.32 (3H, t, *J* = 7.3, OCH$_2$C$\underline{H}_3$); 4.04 (2H, br. s, 3-CH_2), 4.35 (2H, q, *J* = 7.3, OC$\underline{H}_2$CH$_3$); 7.54-8.05 (5H, m, H Ph); NH proton signal is not localized. ^{13}C NMR spectrum (crystalline state), δ, ppm: form $\mathbf{B_E^2}$: 14.7 (OCH$_2$C$\underline{H}_3$); 25.6 (C($\underline{C}$H$_3$)$_3$); 37.4 ($\underline{C}$(CH$_3$)$_3$); 44.6 (3-CH_2); 61.4 (O$\underline{C}$H$_2$CH$_3$); 128.9 (2C), 129.8 (2C), 132.7, 133.3 (C Ph); 144.1 (C=N); 162.2, 164.1 ($\underline{C}$OPh, $\underline{C}O_2$Et); 211.5 ($\underline{C}$OBu-*t*). ^{13}C NMR spectrum (DMSO-d$_6$), δ, ppm: form $\mathbf{B_E^2}$: 15.7 (OCH$_2$C$\underline{H}_3$); 26.8 (C($\underline{C}$H$_3$)$_3$); 42.9 (3-CH_2); 44.7 ($\underline{C}$(CH$_3$)$_3$); 66.2 (O$\underline{C}$H$_2$CH$_3$); 128.1 (2C), 129.3 (2C), 132.7, 133.0 (C Ph); 135.5 (C=N); 162.0, 163.1 ($\underline{C}$OPh, $\underline{C}O_2$Et); 212.6 ($\underline{C}$OBu-*t*). Found, %: C 64.21; H 6.89; N 8.71. $C_{17}H_{22}N_2O_4$. Calculated, %: C 64.13; H 6.97; N 8.80.

Ethyl 5-Methyl-4-oxo-2-[(*Z*)-2-(2-pyridylcarbonyl)hydrazono]hexanoate (3g). Yield 0.384 g (84%); mp 127-128°C. IR spectrum, ν, cm^{-1} (form $\mathbf{B_Z^2}$): 1707, 1696 (CO_2Et, COPr-*i*). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): form $\mathbf{A^2}$ (9%): 3.06 (1H, d, J_{AB} = 18.9) and 3.26 (1H, d, J_{AB} = 18.9, 3-CH_2); other signals in common with the major tautomer or not localized; form $\mathbf{B_Z^2}$ (87%): 1.04 (6H, d, *J* = 6.9, (CH(C$\underline{H}_3$)$_2$); 1.22 (3H, t, *J* = 7.3, CH$_2$C$\underline{H}_3$); 2.51-2.65 (1H, m, C$\underline{H}$(CH$_3$)$_2$); 3.77 (2H, s, 3-CH_2); 4.22 (2H, q, *J* = 7.3, OC$\underline{H}_2$CH$_3$); 7.38 (1H, ddd, *J* = 7.7, *J* = 4.7, *J* = 1.4, H Py); 7.77 (1H, td, *J* = 7.8, *J* = 1.6, H Py); 8.18 (1H, br. d, *J* = 7.6, H Py); 8.55-8.59 (1H, m, H Py); 14.11 (1H, br. s, NH); form $\mathbf{B_E^2}$ (4%): 4.01 (2H, s, 3-CH_2); 11.86 (1H, br. s, NH); other signals in common with major tautomer or not localized. ^{13}C NMR spectrum, δ, ppm (form $\mathbf{B_Z^2}$): 14.3 (OCH$_2$C$\underline{H}_3$); 18.6 (CH($\underline{C}$H$_3$)$_2$); 41.2 ($\underline{C}$H(CH$_3$)$_2$); 46.1 (CH_2); 62.4 (O$\underline{C}$H$_2$CH$_3$); 123.9, 127.4, 137.8, 149.1, 149.3 (C Py); 137.8 (C=N); 161.8, 162.1 ($\underline{C}$OPy, $\underline{C}O_2$Et); 210.8 ($\underline{C}$OPr-*i*). Found, %: C 59.02; H 6.20; N 13.71. $C_{15}H_{19}N_3O_4$. Calculated, %: C 59.01; H 6.27; N 13.76.

Ethyl 5-Methyl-4-oxo-2-[(*Z*)-2-(2-pyridylcarbonyl)hydrazono]heptanoate (3h). Yield 0.429 g (90%); mp 103-104°C. IR spectrum, ν, cm^{-1} (form $\mathbf{B_Z^2}$): 1706, 1696 (CO_2Et, COBu-*s*). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): form $\mathbf{B_Z^2}$ (96%): 0.93 (3H, t, *J* = 7.3, OCH$_2$C$\underline{H}_3$); 1.15 (3H, d, *J* = 7.3, CH(Et)C$\underline{H}_3$); 1.35 (3H, t, *J* = 7.3, OCH$_2$C$\underline{H}_3$);

1.39-1.50 (3H, m) and 1.68-1.80 (3H, m, CH(Me)C$\underline{H}_2$Me); 2.50-2.61 (1H, m, C$\underline{H}$(Me)Et); 3.88 (1H, d, J_{AB} = 18.2) and 3.90 (1H, d, J_{AB} = 18.2, 3-CH_2); 4.35 (2H, q, J = 7.3, OC$\underline{H}_2CH_3$); 7.51 (1H, br. dd, J = 6.9, J = 5.1, H Py); 7.90 (1H, td, J = 7.1, J = 1.4, H Py); 8.31 (1H, d, J = 7.2, H Py); 8.70 (1H, br. d, J = 5.1, H Py); 14.24 (1H, br. s, NH); form $\mathbf{B}_E^2$ (4%): 3.98 (1H, d, J_{AB} = 16.0) and 4.01 (1H, d, J_{AB} = 16.0, 3-CH_2); 11.83 (1H, br. s, NH); other signals in common with the major tautomer or not localized. ^{13}C NMR spectrum, δ, ppm (form $\mathbf{B}_Z^2$): 12.0 (CH_3); 14.3 (CH_3); 16.3 (CH_3); 24.2 (CH(Me)$\underline{C}H_2$); 46.9 (3-CH_2); 48.1 ($\underline{C}$H(Me)Et); 62.5 (O$\underline{C}H_2CH_3$); 123.8, 127.4, 137.8, 149.1, 149.3 (C Py); 137.9 (C=N); 161.8, 162.1 ($\underline{C}$OPy, $\underline{C}O_2$Et); 210.8 ($\underline{C}$OBu-*s*). Found, %: C 60.28; H 6.67; N 13.08. $C_{16}H_{21}N_3O_4$. Calculated, %: C 60.18; H 6.63; N 13.16.

Ethyl 5,5-Dimethyl-4-oxo-2-[(*Z*)-2-(2-pyridylcarbonyl)hydrazono]hexanoate (3i). Yield 0.374 g (78%); mp 134-135°C. IR spectrum (form $\mathbf{B}_Z^2$), ν, cm^{-1}: 1714 (CO_2Et), 1696 (COBu-*t*). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): form $\mathbf{B}_Z^2$ (95%): 1.22 (9H, s, C(CH_3)$_3$); 1.34 (3H, t, J = 7.3, $OCH_2C\underline{H}_3$); 3.97 (2H, br. s, 3-CH_2); 4.34 (2H, q, J = 7.3, OC$\underline{H}_2CH_3$); 7.50 (1H, br. dd, J = 7.9, J = 4.4, H Py); 7.91 (1H, br. t, J = 8.0, H Py); 8.31 (1H, d, J = 8.0, H Py); 8.70 (1H, br. d, J = 4.4, H Py); 14.26 (1H, br. s, NH); form $\mathbf{B}_E^2$ (5%): 1.26 (9H, s, C(CH_3)$_3$); 1.40 (3H, t, J = 7.3, $OCH_2C\underline{H}_3$); 4.07 (2H, br. s, 3-CH_2), 4.40 (2H, q, J = 7.3, OC$\underline{H}_2CH_3$);); 7.50 (1H, br. dd, J = 7.9, J = 4.4, H Py); 7.91 (1H, br. t, J = 8.0, H Py); 8.31 (1H, d, J = 8.0, H Py); 8.61 (1H, br. d, J = 4.4, H Py); 11.81 (1H, br. s, NH). ^{13}C NMR spectrum (form $\mathbf{B}_Z^2$), δ, ppm: 14.3 ($OCH_2\underline{C}H_3$); 26.9 (C($\underline{C}H_3$)$_3$); 43.3 (3-CH_2); 44.6 ($\underline{C}$(CH_3)$_3$); 62.4 (O$\underline{C}H_2CH_3$); 123.9, 127.4, 137.8, 149.1, 149.4 (C Py); 138.4 (C=N); 161.8, 162.1 ($\underline{C}$OPy, $\underline{C}O_2$Et); 212.5 ($\underline{C}$OBu-*t*). Found, %: C 60.20; H 6.64; N 12.91. $C_{16}H_{21}N_3O_4$. Calculated, %: C 60.18; H 6.63; N 13.16.

Ethyl 1-Formyl-5-hydroxy-3-(1,1-dimethylethyl)-4,5-dihydro-1*H*-pyrazole-5-carboxylate (3j) and Ethyl 1-Formyl-5-hydroxy-5-(1,1-dimethylethyl)-4,5-dihydro-1*H*-pyrazole-3-carboxylate (3k). The reaction of ester **1f** with formylhydrazine (**2a)** gave a 2:3 mixture of regioisomers $\mathbf{A}^1$ (ester **3j**) and $\mathbf{A}^2$ (ester **3k**) as indicated by ^{1}H NMR spectroscopy. The mixture could not be separated into pure compounds by recrystallization or thin-layer chromatography. The total yield of these regioisomers was 0.211 g (58%). Mp 74-75°C. Compound **3j**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.24 (9H, s, C(CH_3)$_3$); 1.31 (3H, t, J = 6.6, $OCH_2C\underline{H}_3$); 3.02 (1H, d, J_{AB} = 18.5) and 3.28 (1H, d, J_{AB} = 18.5, 4-CH_2); 4.32 (2H, q, J = 6.6, OC$\underline{H}_2CH_3$); 4.55 (1H, br. s, OH), 8.67 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 14.4 ($OCH_2\underline{C}H_3$); 25.3 (C($\underline{C}H_3$)$_3$); 30.1 ($\underline{C}$(CH_3)$_3$); 44.6 (C-4); 62.7 (O$\underline{C}H_2CH_3$); 87.3 (C-5); 154.8 (C-3); 160.5 (CHO); 164.6 ($\underline{C}O_2$Et). Compound **3k**. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.04 (9H, s, C(CH_3)$_3$); 1.40 (3H, t, J = 7.3, $OCH_2C\underline{H}_3$); 3.14 (1H, d, J_{AB} = 19.8) and 3.42 (1H, d, J_{AB} = 19.8, 4-CH_2); 4.38 (2H, q, J = 7.3, OC$\underline{H}_2CH_3$); 4.55 (1H, br. s, OH), 8.91 (1H, s, CHO). ^{13}C NMR spectrum, δ, ppm: 14.5 ($OCH_2\underline{C}H_3$); 28.3 (C($\underline{C}H_3$)$_3$); 34.5 ($\underline{C}$(CH_3)$_3$); 45.7 (C-4); 63.8 (O$\underline{C}H_2CH_3$); 102.6 (C-5); 148.8 (C-3); 161.4 (CHO); 170.0 ($\underline{C}O_2$Et). Found, %: C 54.42; H 7.41; N 11.43. $C_{11}H_{18}N_2O_4$. Calculated, %: C 54.53; H 7.49; N 11.56.

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