PYRIMIDINES

XLVI.* 2-PYRIMIDOYLACETATE ESTERS

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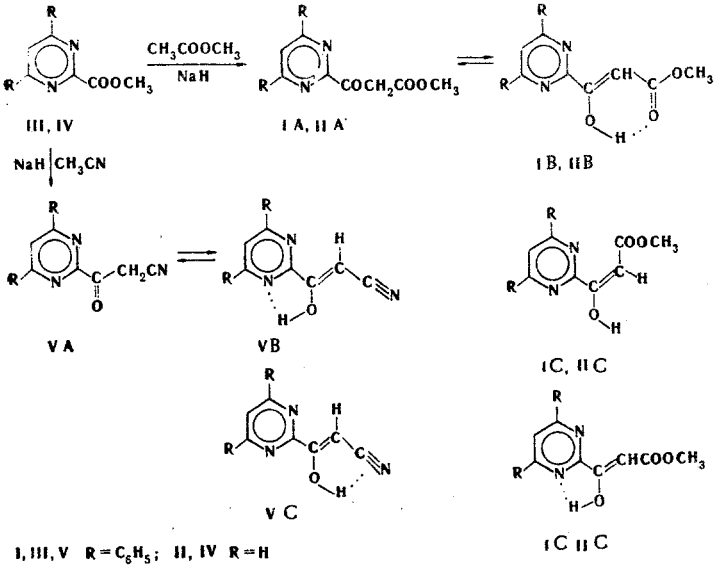
UDC 547.854.2/8:543.422.25.4:541.623

The corresponding 2-pyrimidoylacetate esters (I, II) and 2-pyrimidoyl-acetonitrile (V) were obtained by condensation of pyrimidine-2-carboxylic acid esters with methyl acetate or acetonitrile. The structures of the tautomeric forms were determined by IR and PMR spectroscopy. The effect of a solvent and protonation of the pyrimidine ring on the ketone–enol equilibrium was examined.

The literature contains only a few examples of the synthesis of β-keto esters of azines containing a β-keto ester grouping in the α position relative to the nitrogen atom of the heteroring (for example, see [2, 3]). The tautomeric equilibria have not been studied for known β-keto esters of a number of azines, although the heterocyclic ring may have a substantial effect on the relative percentages of the ketone and enol forms and the structure of the latter.

We have synthesized 2-pyrimidoylacetate esters (I, II) by ester condensation of the corresponding methyl esters of pyrimidine-2-carboxylic acids (III, IV) with methyl acetate in the presence of sodium hydride. Dimethylformamide (DMF), which makes it possible to carry out the reaction in the cold, was used as the solvent for the synthesis of keto ester I, whereas 1,2-dimethoxyethane (monoglyme) was used as the solvent for the synthesis of keto ester II, inasmuch as the use of DMF in this case hindered the isolation of the final product.



*See [1] for communication XLV.

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Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 8, pp. 1136-1140, August, 1975. Original article submitted August 9, 1974.

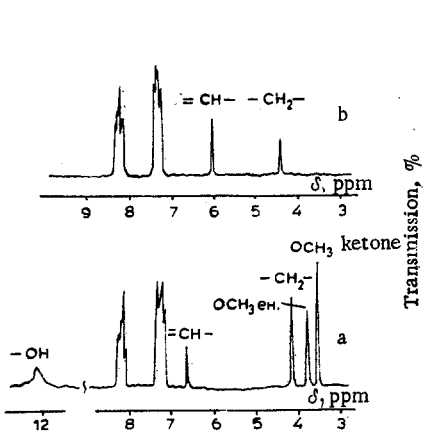


Fig. 1

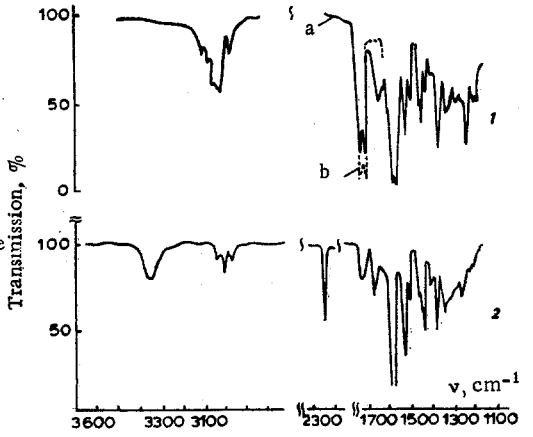


Fig. 2

Fig. 1. PMR spectra of I and V in $CDCl_3$; a) I; b) V.

Fig. 2. IR spectra of I and V: 1a) I in $CHCl_3$; 1b) I in KBr; 2) V in $CHCl_3$.

TABLE 1. Percentage of the Enol Form of β-Keto Esters I and II in Several Solvents (according to the PMR data at 35°C for 3-5% solutions)

Solvent	Percentage of enol I, %	Percentage of enol II, %
CCl_4	>33*	64
$CHCl_3$	33	48
CH_3COCH_3	—	31
DMF	>5	—
CF_3COOH	65	80

Data on the structures of β-keto esters I and II were obtained from an examination of their IR and PMR spectra. In addition to the tautomeric forms A, B, and C (see the scheme above) known for β-dicarbonyl compounds [4], enol form D with a five-membered chelate ring, the presence of which, for example, is discussed for some β-diketones of the pyridine series [5], is possible for I and II.

Absorption bands are absent at 3500-3700 cm^{-1} in the IR spectra of dilute solutions of keto ester I in $CHCl_3$ and CCl_4, and this excludes the unlikely trans-enol form C with a free OH group from consideration. Signals of protons of ketone and enol forms (~ 30% enol), signals of aromatic protons, and a broad signal of an OH proton are observed in the PMR spectrum of I in $CDCl_3$ solution (Fig. 1). The IR spectrum of a KBr pellet of I (Fig. 2, spectrum 1b) contains bands of carbonyl absorption that are characteristic for the ketone (1720 cm^{-1}) and ester (1740 cm^{-1}) groups of β-keto esters. In the IR spectrum of a $CHCl_3$ solution of I (Fig. 2, spectrum 1a) the intensity of the carbonyl absorption bands is reduced substantially as compared with the IR spectrum in KBr, and a broad intense band appears at 1615-1670 cm^{-1}, which is characteristic for six-membered rings with an intramolecular hydrogen bond (IHB), formed during the enolization of β-dicarbonyl compounds [6]. On the basis of the above-noted changes in the IR spectrum and proceeding from the δ_{OH} value (~ 12 ppm) in the PMR spectra, which is characteristic for six-membered chelates of β-keto esters [4], one may assert that the predominant form is enol form B, although one cannot exclude the simultaneous presence of a small amount (~30% of B) of enol form D.

The final conclusions were made on the basis of a study of the spectral data for 4,6-diphenyl-2-pyrimidoylacetonitrile (V), synthesized by condensation of ester III with acetonitrile under the case conditions as in the preparation of keto ester I. The PMR spectrum of this compound in $CDCl_3$ (Fig. 1, spectrum 2) indicates strong enolization (~80% of the enol), which is also retained in the solid state (the IR spectrum of a KBr pellet contains low-intensity absorption at 1735 cm^{-1}). The IR spectra of solutions of V in $CHCl_3$ and CCl_4 (Fig. 2, spectrum 2) contain an absorption band at 3350-3370 cm^{-1}; absorption bands are absent at higher frequencies. The small amount of dependence of the position of this band on the concentration and the character of the solvent constitutes evidence for the participation of the enol hydroxyl group in an IHB, whereas the frequency of the band indicates that structure VB with a five-membered chelate ring is realized. It should be noted that for a weak IHB with the π electrons of the nitrile group (structure VC) one

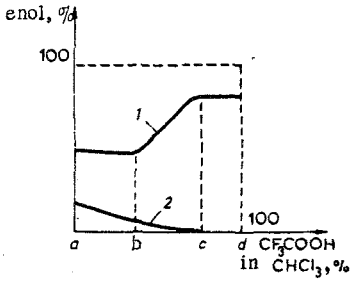
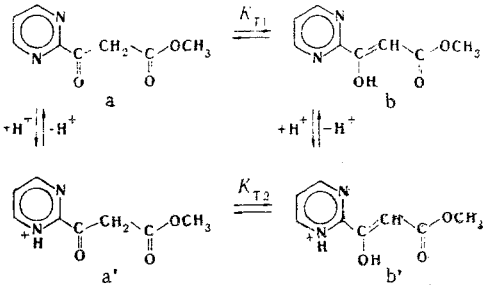


Fig. 3. Dependence of the percentage of the enol form on the percent CF_3COOH in $CDCl_3$: 1) 2-pyrimidoylacetate ester; 2) benzoyl acetate ester.

should have expected a much higher ν_{OH} absorption frequency [7], whereas an IHB with the nitrogen atom of the C ≡ N group is impossible for V for steric reasons. Inasmuch as the IR spectra of solutions of keto ester I in $CHCl_3$ and CCl_4 do not contain absorption bands at 3200-3700 cm^{-1} it may be concluded that enol structure ID is practically absent and that the equilibrium IA ⇌ IB exists in solution. Pyrimidoylacetate ester II has similar spectral characteristics, and, as for I, equilibrium IIA ⇌ IIB is characteristic for it. Our results and the data in [8, 9] regarding the relatively small change in ν_{OH} (and consequently, the strength of the IHB) for various five-membered chelates make it possible to assume that an enol structure of the ID type also will not be realized for other β-keto esters of the azine series.

We studied the effect of the solvent on the position of the tautomeric equilibrium for β-keto esters I and II (see Table 1).



Unsubstituted pyrimidoylacetate ester II is enolized to a greater degree than I in all of the examined solvents. As in the case of other β-keto esters, the percentage of the enol decreases as the polarity of the solvent increases. However, the percentage of the enol form in trifluoroacetic acid sharply increases as compared with the other solvents. The qualitative picture of the dependence of the percentage of the enol form of the 2-pyrimidoylacetate ester (curve 1) and benzoyl acetate ester (curve 2) on the percentage of trifluoroacetic acid in a mixture with $CHCl_3$ (according to the PMR spectra) is presented in Fig. 3. Considering that the pyridimidine derivatives can be protonated in trifluoroacetic acid [10], this dependence can be explained as follows.

Tautomeric equilibrium ⇌ b is characteristic for segment ab (Fig. 3), and the percentage of the enol form decreases somewhat as the percent CF_3COOH increases because of deterioration of the conditions for its solvation [4]. The role of protonation increases in segment bc, two ketone–enol equilibria (a ⇌ b and a' ⇌ b') exist in solution, and the contribution of the latter increases as the CF_3COOH concentration increases. Inasmuch as the two ketone forms (a and a') and the two enol forms (b and b') exist under conditions of rapid proton exchange, signals of two forms are observed in the PMR spectra: overall signals of the ketone forms and overall signals of the enol forms, averaged with respect to their shifts and totalled with respect to their intensities. As a consequence of this, a gradual shift of the signals in the PMR spectrum to weak field (by 0.2-0.3 ppm) is observed as the relative weight of equilibrium a' ⇌ b' increases. This shift ceases as the CF_3COOH concentration approaches c, and this constitutes evidence for complete protonation; segment cd is subsequently characterized by tautomeric equilibrium a' ⇌ b'. It is not difficult to show that $K_{T2} = K_{T1}(K_{base\ b}/K_{base\ a})$, where K_{T1} and K_{T2} are the corresponding constants of the tautomeric equilibria, and $K_{base\ a}$ and $K_{base\ b}$ are the basicity constants of tautomers a and b. It may be assumed that $K_{base\ b} > K_{base\ a}$, and then $K_{base\ b}/K_{base\ a} > 1$ and $K_{T2} > K_{T1}$, i.e., one should expect a high degree of enolization for equilibrium a' ⇌ b', and this is observed from the PMR data. Thus protonation of the heteroring in our case has a such greater effect on the position of the tautomeric equilibrium than the simultaneously operating solvation factor, which tends to shift the equilibrium to favor the ketone form.

The chemical properties of the 2-pyrimidoylacetate esters will be described separately.

EXPERIMENTAL METHOD

The IR spectra were recorded with UR-10 spectrometer. The PMR spectra were recorded with an A-56/60A spectrometer (δ scale) with tetramethylsilane as the external standard.

4,6-Diphenyl-2-pyrimidoylacetate Ester (I). S 0.86-g (0.036 mole) sample of sodium hydride was added to a solution of 8.7 g (0.03 mole) of III [11] in 45 ml of DMF, and a solution of 2.5 ml (0.031 mole) of methyl acetate in 10 ml of DMF was added dropwise in the course of 5 h to the stirred suspension. The mixture was stirred for another hour, the residual sodium hydride was decomposed with 1.5 ml of methanol, and the mixture was poured into 250 ml of water. The resulting fine precipitate of the sodium salt of I was coagulated by rapid heating to 60-70° with stirring, and the resulting precipitate was removed by filtration, vacuum dried over P_2O_5, washed on the filter with 40 ml of chloroform, and redried. The dry salt (6.5 g) was dispersed in 100 ml of petroleum ether and acidified with a mixture of 3 ml of acetic acid and 0.6 ml of concentrated HCl. The mixture was stirred vigorously until the yellow color of the solid disappeared (usually 30 min). The solid was removed by filtration, vacuum-dried, washed thoroughly with water, and redried in vacuo over P_2O_5 to give 5.6 g of I (55%) with mp 120-125°. Recrystallization from petroleum ether (bp 70-100°) gave a product with mp 122-125°. Found: C 72.1; H 4.59; N 8.28%. $C_{20}H_{16}N_2O_3$. Calculated: C 72.3; H 4.85; N 8.43%.

4,6-Diphenyl-2-pyrimidoylacetonitrile (V). This compounds was synthesized as in the preceding experiment using acetonitrile in place of methyl acetate and reducing the dropwise addition time to 2 h. The precipitated sodium salt was removed by filtration and, without coagulation, was worked up as in the preceding experiment to give V with mp 155-160° (from acetone) in 67% yield. Found: C 76.2; H 4.14; N 13.8%. $C_{19}H_{13}N_3O$. Calculated: C 76.2; H 4.38; N 14.0%.

2-Pyrimidoylacetate Ester (II). A 0.29-g (0.012 mole) sample of NaH was added to a solution of 1.38 g (0.01 mole) of IV [11] in 25 ml of monoglyme, and a solution of 0.85 ml (0.0105 mole) of methyl acetate in 5 ml of monoglyme was added dropwise in the course of an hour to the stirred suspension. After this, two to three drops of methanol were added, the temperature of the mixture was raised to 80°, and it was stirred at this temperature for 3 h. It was then cooled, and the resulting yellow precipitate was separated by centrifugation. It was then stirred thoroughly with a mixture of 20 ml of monoglyme and 0.3 ml of methanol (for decomposition of the residual NaH), after which it was again centrifuged. The resulting sodium salt of the β-keto ester was vacuum-dried. The dry salt (2 g) was added in small portions to acetic acid containing dry HCl (10 ml of glacial acetic acid was saturated with 0.6 g of dry HCl), and the bulk of the solvent was removed in vacuo. The residual oil was tirturated with 5 ml of chloroform and passed through a column (10 by 150 mm) containing silica gel with elution by benzene–ether (1:1) to give a fraction that gave a red coloration with $FeCl_3$ solution. Removal of the solvent in vacuo gave 0.9 g (50%) of II with mp 56-61° (from CCl_4–petroleum ether). Found: C 54.0; H 4.27; N 15.5%. $C_8H_8N_2O_3$. Calculated: C 53.3; H 4.48; N 15.5%. IR spectrum in KBr, ν, cm^{-1}; 1730 (ketone C = O) and 1745 (ester C = O).

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