TAUTOMERISM OF 1-PHENYL-3-METHYL-4-BENZYL-5-PYRAZOLONE

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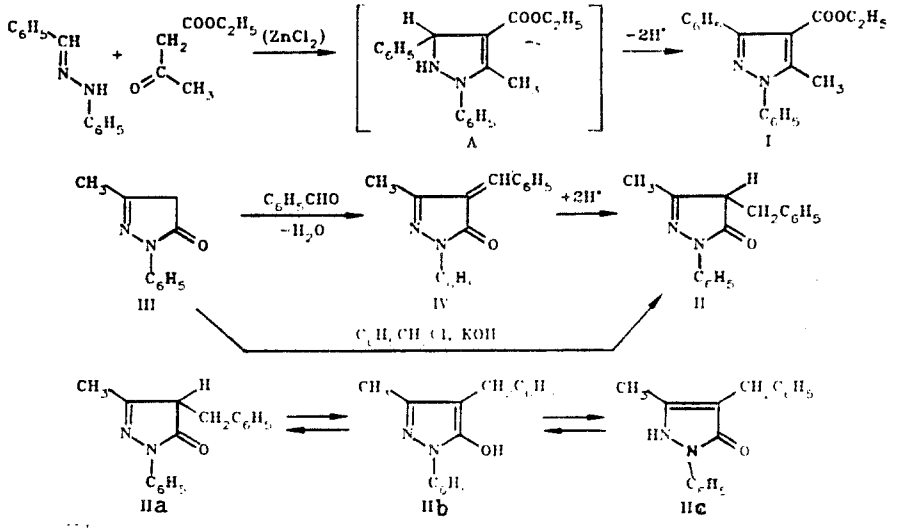
The tautomerism of 1-phenyl-3-methyl-4-benzyl-5-pyrazolone — a side product in the reaction of acetoacetic ester with benzaldehyde phenylhydrazone — was studied by IR and PMR spectroscopy, and its thermodynamic characteristics were determined.

The reaction of acetoacetic ester with benzaldehyde phenylhydrazone is used in the synthesis of ethyl 1,3-diphenyl 5-methylpyrazole-4-carboxylate (I) [1]. Our repetition of this reaction showed that another reaction product, in addition to I, which is formed in low yield, is obtained in significant amounts; we proved its structure as pyrazolone II by elementary analysis, investigation of its chemical properties (solubility in alkalis), spectral data, and alternative synthesis — by benzylation of 1-phenyl-3-methyl-5-pyrazolone (III) by the method in [2]. In the case of intensive removal of water from the reaction mixture the yield of pyrazole I reached 59%, and the percentage of pyrazolone II decreased. The starting hydrazone is probably partially hydrolyzed in the presence of $ZnCl_2$ to give benzaldehyde and phenylhydrazine; the latter reacts with acetoacetic ester to give pyrazolone III, which reacts with benzaldehyde to give 1-phenyl-3-methyl-4-benzylidene-5-pyrazolone (IV) [3]. The active hydrogen liberated as a result of the spontaneous dehydrogenation of the unstable intermediate pyrazoline (A) reduces derivative IV to II.



To confirm this scheme for the formation of pyrazolone II we added 1 mole of pyrazolone IV to the reaction mixture. Analysis of the reaction mass by GLC showed that benzylpyrazolone II is formed in 15.9% yield, whereas the yield is 1% in a control experiment without the addition of IV.

It has been previously established [4] that the substituents in the 4 position of the ring significantly change the tautomeric equilibrium, shifting it to favor either the pyrazolone or the hydroxypyrazole. The tautomeric properties of pyrazolone II, for which existence in three forms (IIa, IIb, and IIc) is permissible, have not been studied, and identification of the tautomeric forms and measurement of the thermodynamic characteristics of the equilibrium of IIa, b, c in solution in dioxane were therefore among the tasks of the present research.

Two sets of signals of methyl groups, methylene protons, and protons of the aromatic part of the molecule are observed in the PMR spectrum of pyrazolone II in d_8-1,4-dioxane at 20°C. The doublet signal at 1.94 ppm with J ~

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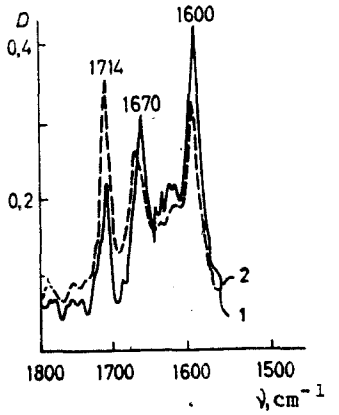


Fig. 1. IR spectra of 1-phenyl-3-methyl-4-benzyl-5-pyrazolone in solution in dioxane (c = 0.1 mole/liter, l = 0.1 mm) at: 1) 15°C; 2) 75°C.

TABLE 1. Frequencies and Integral Intensities of IIa-c and Model Compounds V and VI at 1500-1750 cm^{-1}

Compound	Solvent	ν (I_{int}, $mole^{-1} \cdot liter \cdot cm^{-2}$)*	Compound	Solvent	ν (I_{int}, $mole^{-1} \cdot liter \cdot cm^{-2}$)*
V	Dioxane	1710 (4,25); 1600 (0,95)	IIb	Dioxane	1600 (1,67)
VI	Dioxane	1677 (6,3); 1600 (0,92)		DMSO	1597 (2,43)
	DMSO	1664 (7,7); 1594 (1,3)		Pyridine	1600 (2,48)
	Pyridine	1670 (6,6); 1595 (1,2)	IIc	Dioxane	1670 (2,01)
IIa	Dioxane	1715 (1,02)		DMSO	1651 (4,04)
				Pyridine	1660 (2,54)

*ν is the frequency, and I_{int} is the integral intensity.

1 Hz and the multiplets at 3.16 and 7.8 ppm attest to the existence of pyrazolone form IIa with a percentage in the mixture of ~25%. The singlet signals of the protons of CH_3 and CH_2Ph groups at 2.0 and 3.6 ppm, respectively, should be ascribed to another tautomeric form or to the averaged state of sufficiently rapidly interconverting forms IIb and IIc. The presence of a broad signal of an exchange proton at 8.7 ppm constitutes evidence in favor of the indicated reversible process. A similar pattern is observed in the PMR spectrum of a solution in d_6-acetone: signals of methyl and methylene protons in a ratio of 1:7 of tautomers IIa and IIb + IIc are found at 2.06 and 2.1 ppm and at 3.25 and 3.65 ppm, respectively.

There are some differences in the PMR spectrum of pyrazolone II in solution in $CDCl_3$ — here three complexes of signals are observed immediately. Tautomeric form IIa makes the chief contribution, and signals of a CH_3 group (J ~0.8 Hz) at 2.0 ppm and multiplets of CH_2 at 3.25 ppm and CH at 3.55 ppm correspond to it. The contribution of the other form (presumably IIc), which gives signals at 2.1 and 3.65 ppm, respectively, is considerably smaller. The third form IIb is seen as a small impurity amounting to < 5% (signal of a methyl group at 1.92 ppm). When the temperature is decreased to −30°C, the intensity of the signal at 1.92 ppm in the PMR spectrum increases, while the corresponding signals of the other forms decrease in intensity.

Absorption bands at 1714 and 1670 cm^{-1}, which can be ascribed to $\nu_{C=O}$ absorption of pyrazolone form Ia and pyrine form IIc, respectively, are observed in the IR spectra of pyrazolone II in solution in dioxane. Confirmation of the existence of tautomeric form IIb (when c = 0.05-0.25 mole/liter) follows from data on the integral intensities of the bands (at 1500-1750 cm^{-1}). In fact, the $\nu_{C=O}$ intensities for the pyrazolone and pyrine forms, which are, respectively, 1.50 ± 0.5 and 2.35 ± 0.6 practical units, are unusually low, being inferior to those for the model compounds (synthesized by the method in [5]) 1-phenyl-3,4-dimethyl-4-benzyl-5-pyrazolone (V) (4.25) and 1-phenyl-2 benzyl-3,4-dimethyl-5-pyrazolone (VI) (6.3) in the same solvent by a factor of 2.5-3. On the other hand, the intensity at 1600 cm^{-1}, which is 1.83 ± 0.3, exceeds the intensities for the indicated models (0.92 and 1.3, respectively) by a factor of 1.5-2. We assume that the absorption at 1600 cm^{-1} is related to the vibrations of the multiple bonds of both the benzene and pyrazole rings. This is confirmed by the change in intensity as a function of the temperature and solvent. Thus the peak intensity of the band at 1714 cm^{-1} increases sharply with an increase in the temperature from 15°C to 75°C, while the intensities of the bands at 1670 and 1600 cm^{-1}, on the other hand, decrease (see Fig. 1). The bonds of intermolecular associates of the solvent (dioxane) with tautomeric forms IIb and IIc, which contain a hydrogen atom

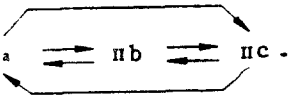
TABLE 2. Experimental ΔH and ΔS Values for Pyrazolone II in Dioxane*

Type of equilibrium	ΔH, cal/mole**	$\sigma(\Delta H)$**	ΔS, cal/deg**	$\sigma(\Delta S)$**
IIa ⇌ IIb	−3000 (−3400)	370 (450)	−8,7 (−9,4)	1,1 (1,3)
IIa ⇌ IIc	−2800 (−3600)	300 (510)	−8,9 (−11)	0,8 (1,6)
IIc ⇌ IIb	−340 (340)	70 (60)	−0,4 (2,1)	0,08 (0,3)

*$\sigma(\Delta H)$ is the mean-square deviation of ΔH; $\sigma(\Delta S)$ is the mean-square deviation of ΔS.
**The values were obtained for c = 0.1 mole/liter; the values obtained for c ~ 0.05 mole/liter are indicated in parentheses.

attached to a heteroatom, evidently undergo partial cleavage on heating, which promotes stabilization of form IIa to the detriment of forms IIb and IIc. An even sharper increase in the relative percentage of form IIa is observed in low polarity aprotic solvents ($CHCl_3$, CCl_4, tetrachloroethylene, benzene), which confirms the PMR spectroscopic data. For example, the peak absorption intensity in solution in benzene at 1714 cm^{-1} is approximately the same as in the spectrum of IIc in solution in dioxane at 75°C (see Fig. 1). In strongly polar solvents (DMSO and pyridine) the absorption of pyrazolone form IIa at 1714 cm^{-1} is completely absent in the spectra of II; one observes the most intense absorption at 1651-1660 and 1597-1600 cm^{-1} of the pyrine and enol forms, respectively (Table 1).

Let us note that the band at 1670 cm^{-1} is shifted toward the higher-frequency side upon dilution or with a decrease in the polarity of the solvent; on the other hand, the position of the band at 1600 cm^{-1} does not depend on the nature of the solvent. Moreover, its use for the direct determination of the percentage of the enol form based on the assumption of equality of the molar absorption coefficients of the tautomer and its O-fixed model is hindered, not only because of the above-indicated overlapping of the absorption of the pyrazole and benzene rings but also because of the uncertainty of the verifying test for the integral intensity of the pyrazolone form (because of the presence also of the pyrine form). However, the fact of shifting of the absorption band of the pyrazole ring from the analytical region (1550-1565 cm^{-1}; see [4]) of 1,3-substituted 5-hydroxypyrazole absorption to the region of benzene absorption (1600 cm^{-1}) is of interest in itself. Let us also note the similarity in the absorption of IIb and IIc and that of the enol forms of acetoacetic or formylmalonic ester, the spectra of which in nonpolar solvents contain absorption with a half width of 100-150 cm^{-1} at 2500-3000 cm^{-1} [6, 7]. The decrease in the pyrazolone form (1714 cm^{-1}) and the increase in the pyrazole and pyrine forms (1600 and 1670 cm^{-1}) in the spectra of II in pyridine (see Table 1), in which the absorption at 2500-3000 cm^{-1} is most strongly expressed, served as an indication that this absorption belongs to the overall absorption for forms IIb and IIc. From an analysis of the relative intensities (see Fig. 1) it is apparent that at 15°C (c = 0.1 mole/liter) the percentages of all of the forms differ and amount to roughly 45% for IIb, 40% for IIc, and 15% for IIa. At 75°C the percentage of form IIa becomes the same as that of form IIb (40% each). Form IIb with intermolecular hydrogen bonds (2500 cm^{-1}) predominates in the crystalline state.

We also determined the thermodynamic characteristics of the equilibria 

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From the data in Table 2 it may be concluded that all three types of tautomeric equilibria are determined virtually completely by the enthalpy factor; the first two equilibria are exothermic (ΔH < 0), and their enthalpies exceed the enthalpy of the conversion of IIc to IIb by an order of magnitude. The latter transition is the easiest, since it is realized between forms with aromatic and partially aromatic properties; the tautomeric transformation becomes endothermic (ΔH > 0; see Table 2) with a decrease in concentration, thereby confirming intermolecular proton transfer.

Thus, with respect to its effect on the tautomeric equilibrium, the benzyl radical, the effect of which approaches that of the cyanoethyl group [4], occupies an intermediate position between phenyl and alkyl radicals. Its effect is extended approximately equally (in dioxane) to all three centers responsible for the tautomeric transitions.

EXPERIMENTAL

Analysis by GLC was carried out with a modified LKhM-8MD chromatograph with a 20 m by 0.2 mm glass column packed with an OV-101 stationary liquid phase; the thermostat temperature was 200°C, the vaporizer temperature was 250°C, and the pressure at the outlet was 0.2 kg/cm^2. The retention times of I, II, and IV were 8.45, 5.01, and 9.30, respectively. The PMR spectra were recorded with a Bruker AC-250 spectrometer with tetramethylsilane (TMS) as the internal standard. The IR spectra of the compounds in the crystalline state and in solution were recorded with a Perkin—Elmer 580 spectrometer; the measurements of the intensities of the absorption bands of the solutions were

made both under automatic conditions by means of the REAK subprogram of the information-search system of the spectrometer and an Interdate 6/16 minicomputer [8] and manually at 15°C to 95°C in conformity with the method in [9]. The calculations were made on the basis of the formulas

$$\ln[D_{11b}(T)/D_{11a}(T)] = (\Delta S_{11b,a}/R) - (\Delta H_{11b,a}/RT);\ \ln[D_{11c}(T)/D_{11a}(T)] = (\Delta S_{11c,a}/R) - (\Delta H_{11c,a}/RT),$$

where D(T) are the optical densities of tautomers IIa,b,c at temperature T, and ΔS and ΔH are the differences in the entropies and enthalpies of the tautomeric forms of II. The cuvettes were equipped with AgCl windows and were thermostatted electrically by means of a Specak 20-100 controller (Perkin—Elmer).

Ethyl 1,3-Diphenyl-5-methylpyrazole-4-carboxylate (I). A) (Experiment with removal of the water by azeotropic distillation.) The flask was charged with 9.81 g (0.05 mole) of benzaldehdye phenylhydrazone, 13.02 g (0.1 mole) of freshly distilled acetoacetic ester, and 0.2 g of anhydrous zinc chloride. Benzene (60 ml) was added, and the mixture was refluxed for 2 h. The benzene and excess acetoacetic ester were removed by vacuum distillation, and alcohol was added to the residue to give 3.9 g of ester I. Another 5.2 g (59.5%) of the ester precipitated from the mother liquor on standing (at 3-5°C) for several days. The product had mp 104-105°C (mp 105°C [1]). The overall yield was 9.1 g.

B) (Experiment in an open flask.) The flask was charged with the reactants as in the preceding experiment; 19.53 g (0.15 mole) of acetoacetic ester was used, and the reaction time was 2.5 h. Workup gave 8.9 g (58%) of ester I with mp 105-106°C.

C) 1. A three-necked flask equipped with a stirrer, a capillary that did not extend to the reaction mass, and an adapter connected to a water aspirator joined through a T-bend for the admission of air was charged with the reactants as in experiment A. The reaction mass was heated to 125-128°C (bath temperature) and maintained at this temperature for 5 h. It was then cooled to ~50°C, after which 15 ml of alcohol was added, a seed crystal of I was introduced, and the mixture was maintained at 0°C (−4°C) for 16 h. It was then filtered to give 6.68 g (43.6% based on the benzaldehyde phenylhydrazone) of I with mp 104-105°C.

2. The yield of I was 25-31% when the experiment was carried out in a flask equipped with an air condenser [1].

3. The use of a water reflux condenser led to a sharp decrease in the yield of ester I.

D) The reaction was carried out as in experiment C but with the addition of 1.8 g of water. Filtration gave 6.2 g of a precipitate with mp 81-90°C (a mixture of ester I and the starting hydrazone). A 5-g sample of II with mp 136-137°C (from alcohol) (mp 136-137°C [2]) was isolated from the mother liquor on standing (at 3-5°C).

1-Phenyl-3-methyl-4-benzyl-5-pyrazolone (II). A 1.74-g (0.01 mole) sample of III [3] was added to a solution of 0.56 g (0.01 mole) of potassium hydroxide in 12 ml of water, after which 1.26 g (0.01 mole) of benzyl chloride was added dropwise with stirring, and the mixture was stirred for 15 h. It was then acidified with dilute HCl, and the solution was decanted from the oily precipitate, which was treated with alcohol and ether. The resulting crystals were removed by filtration and recrystallized from alcohol to give a product with mp 136-137°C. No melting-point depression was observed for a mixture of this product with the II obtained by method D, and the IR spectra (solutions in chloroform) of the two samples were identical.

Compound II was previously synthesized by condensation of α-benzylacetoacetic ester with phenylhydrazine [10] or by catalytic reduction of IV [11].

1-Phenyl-3-methyl-4-benzylidene-5-pyrazolone (IV). A mixture of 5.22 g (0.03 mole) of III and 4.77 g (0.045 mole) of benzaldehyde was heated at 125-128°C for 2.5 h. The next day the crystallized mass was treated with alcohol, and the precipitate was removed by filtration and recrystallized from alcohol to give 5.35 g of red crystals of IV with mp 106-107°C (mp 106-107°C [3]).

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