TAUTOMERISM OF AZINE DERIVATIVES.

5.* EFFECT OF THE HETEROATOM ON THE KETO-ENOL TAUTOMERISM OF β-KETO ESTERS OF THE AZINE SERIES

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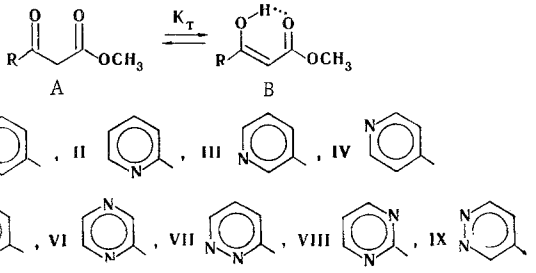
The effect of a nitrogen atom in various positions of the heteroaromatic ring on the ketol-enol equilibrium of 2-, 3-, and 4-pyridoyl-, 2- and 4-pyrimidoyl-, pyrazinoyl-, and 3- and 4-pyrazinoylacetic esters is examined. The "anomalous" effect of a nitrogen atom on the α position relative to the tautomeric fragment is noted and is explained by interaction of the unshared pair of the nitrogen atom with the orbitals of the carbonyl group, which may lead to a decrease in the acceptor character of the azine substituent.

In the study of heterocyclic systems it is important to have an understanding of the role of the electronic effects of the heteroatom, which substantially determines both the properties of the heteroring and its properties as a substituent with respect to the side chain.

We have previously [1] synthesized aza analogs of benzoylacetic ester (II-VIII) and have investigated their structures and ketol-enol tautomerism in various solvents. β-Keto esters are extremely convenient models for the study of the effects of a heteroatom in various positions of the aromatic ring on the position of the tautomeric equilibrium. On the one hand, a single type of tautomeric equilibrium (A $\rightleftharpoons$ B) with comparable percentages of both forms is realized for all of the examined compounds in neutral nonpolar solvents, and this makes it possible to determine with a high degree of accuracy the difference in the free energies (ΔG) of the tautomers. On the other hand, the change in the entropy (ΔS) for the tautomerism of such compounds is virtually independent of the changes in the aromatic ring, and this makes it possible to regard the effect introduced by the heteroatom (ΔΔG) as enthalpic (i.e., electronic) in nature.



The change in the position of the tautomeric equilibrium when a heteroatom is introduced (for example, on passing from benzoylacetic ester to γ-pyridoylacetic ester) can be evaluated within the framework of the simple valence molecular orbital (VMO) method.

*See [1] for Communication 4. In Communication 4 [Khim. Geterotsikl. Soedin., No. 6, p. 823 (1980)] there is a misprint in the scheme that illustrates the tautomeric equilibrium β-keto esters with the participation of protonated forms. See [16] for the corrected scheme.

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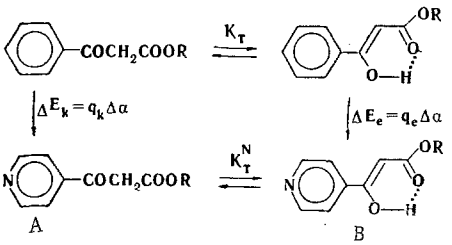
Scheme



The energy effect when a =CH fragment in the benzene ring is replaced by a heteroatom can, according to [2], be described by expression (1):

$$\Delta E = \Sigma q_i \Delta\alpha_i + 2\Sigma\Sigma_{i>j} p_{ij} \Delta\beta_{ij}, \quad (1)$$

where q_i is the π-electron density, $\Delta\alpha$ is the change in the Coulombic integral, p_{ij} is the bond order, and $\Delta\beta$ is the change in the resonance integral.

The close values of the C=C and C=N bond orders [3] and the force constants of the stretching vibrations of these bonds [4] makes it possible to assume $\Delta\beta = 0$ (see also [5]). In this case, the energy effect (disregarding the increase in the electronegativities of the adjacent carbon atoms as a consequence of the I_π effect of the heteroatom) can be evaluated for the enol (e) and keto (k) forms, respectively, as

$$\Delta E_e = q_e{}^i \Delta\alpha,\ \Delta E_k = q_k{}^i \Delta\alpha,\ \Delta\Delta E = \Delta\alpha (q_e{}^i - q_k{}^i). \quad (2)$$

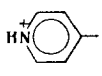
Thus the shift in the tautomeric equilibrium when a heteroatom is introduced can be predicted if one knows the ratio of the π-electron densities at the site of introduction of the heteroatom — in this case (see Scheme) in the para position of the benzene ring of the A and B forms.

When electron-acceptor substituents of the +E type such as keto and enol fragments are introduced in the benzene ring, the electron density of the benzene ring is lowered, particularly in the ortho and para positions [6, 7]. The σ^+ values of the ketone and enol fragments that we determined in [1] indicate the substantially greater acceptor character of the ketone fragment as compared with the enol fragment ($\sigma_k{}^+ = 0.61$; $\sigma_e{}^+ = 0.34$) and, consequently, the higher electron density in the benzene ring of the enol form ($q_e{}^i$) as compared with the keto form ($q_k{}^i$), in agreement with the calculated data [1]. This charge ratio ($q_e > q_k$) means that on passing from benzoylacetic ester to γ-pyridoylacetic ester the equilibrium should be shifted to favor the enol. It is evident that the $q_e > q_k$ ratio will also be retained for pyridoylacetic esters II and III, as a consequence of which the transition to their γ-aza analogs V and IX should also be accompanied by an increase in the enol fraction.

These conclusions are in good agreement with the experimental data obtained for azinoylacetic esters II-IX. Thus for each of the pairs I and IV, II and V, and III and IX the tautomeric equilibrium of γ derivatives IV, V, and IX is characterized by a greater K_t value (Table 1). It follows from Table 1 that the introduction of a nitrogen atom in the γ position increases the enol fraction by ∿40%, which corresponds to changes of ∿1 kcal/mole in the ΔG value.

When a heteroatom is introduced in the α and β positions of an aromatic ring, one might also expect an increase in the degree of enolization. Although the dependence of the electron density in the α and β positions of an aromatic ring on the acceptor character of the substituent is more complex, one may, however, assume [6, 7] that for these positions also the increase in the acceptor character of the introduced substituent leads to a decrease in the electron density. For example, the ^{13}C NMR chemical shifts for the α- and β-carbon atoms of the keto form of the γ-pyridoylacetic ester are found at weaker field as compared with the signals of the enol form [1], which is in agreement with the greater acceptor character of the keto fragment. In evaluating the energic effect of the introduction of a heteroatom in the β position one must take into account the fact that, although the difference in the electron densities for the keto and enol forms in this position is small, the introduction of a nitrogen atom will give rise to an appreciable increase in the electronegativity (an increase in the α coulombic integral) of the adjacent carbon atoms. In conformity with expression (1), this will lead to additional stabilization of the enol form,

TABLE 1. Effect of the Position of the Nitrogen Atom in the Heteroaromatic Ring on the Keto-Enol Equilibrium

	R in the "precursor" molecule	% enol* (ΔG, kcal/mole) ($CDCl_3$)	R in the molecule with a nitrogen atom	% enol* (ΔG, kcal/mole) ($CDCl_3$)	Difference in the enol content, %	$\Delta\Delta G$, kcal/mole
γ-atom		17 (0,97)		57 (−0,17)	40	−1,14
		17 (0,97)		55 (−0,12)	38	−1,09
		35 (0,35)		76 (−0,71)	41	−1,06
β-Atom		17 (0,97)		35 (0,35)	18	−0,62
		17 (0,97)		35 (0,35)	18	−0,62
		57 (−0,17)		76 (−0,71)	19	−0,54
α-Atom		17 (0,97)		17 (0,97)	0	0
		57 (−0,17)		55 (−0,12)	−2	0
		35 (0,35)		35 (0,35)	0	0
		17 (0,97)		50 (0)	33	−0,97
		35 (0,35)		21 (0,81)		+0,46
Protonation		17		60†		
		17		85†		

*See [1, 16, 20].
†For a CF_3COOH—$CDCl_3$ mixture.

since $q_e^{\alpha,\gamma} > q_k^{\alpha,\gamma}$. Thus starting from expressions (1) and (2) one may expect an increase in the degree of enolization also when a heteroatom is introduced in the α and β positions of the aromatic ring.

An analysis of the experimental data on the tautomeric equilibrium of I-IV, VI, and IX confirms this conclusion for compounds with a β heteroatom (Table 1). The introduction of a heteroatom in the β position leads to an increase in the enol content of ∿20% ($\Delta\Delta G$ = 0.6 kcal/mole).

One might have expected that the introduction of a heteroatom in the α position would also increase the enol fraction (in conformity with the expression $q_e^{\alpha} > q_k^{\alpha}$). However, the

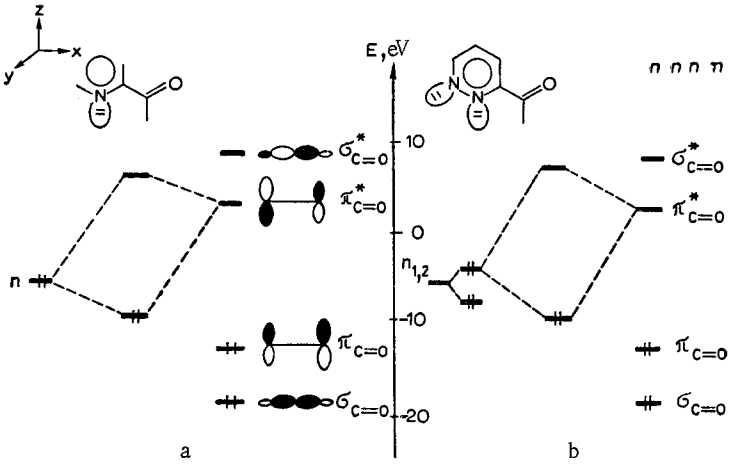


Fig. 1. Interaction of the unshared pair of electrons of the nitrogen atom with the vacant orbitals of the C=O group of pyridoyl- (a) and 3-pyridazinoylacetic (b) esters. The energies were estimated by the CNDO/2 method (standard geometry), and data from *ab initio* calculations were also used [19].

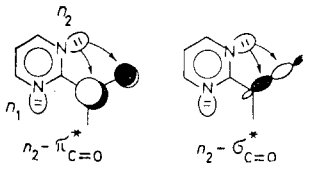


Fig. 2. Interaction of the unshared pair of the nitrogen atom (n_2 is "cis" with respect to the oxygen atom) with the orbitals of the carbonyl group in 2-pyrimidoylacetic ester.

effect of an α heteroatom proved to be different than that expected: It is apparent from Table 1 that the enol content remains virtually unchanged. The effect of an α-nitrogen atom thus differs substantially from the effect of β- and γ-nitrogen atoms. It is important to note that in the absence of an unshared pair of electrons an increase in the electronegativity of the α position increases the enolizability. Thus for protonated α- and γ-pyridoylacetic esters the introduction of an $=NH^+$ fragment in both the γ and α positions increases equally markedly the enol fraction as compared with benzoylacetic ester (Table 1).

To explain the "anomalous" effect of an α-nitrogen atom we assumed (Fig. 1a) that the factor that acts counter to the increase in the enol fraction is the additional stabilization of the keto form due to interaction of the unshared pair of the nitrogen atom with the vacant orbitals of the carbonyl group (for example, see [8, 9]). An analysis of this orbital interaction from the point of view of symmetry shows that, depending on angle θ, interaction of the unshared pair of the nitrogen atom either with σ* (θ = 0, 180°) or with the σ* and π* orbitals (θ ≠ 0, 180°) is possible. It should be noted that interaction of the orbitals is less favorable for a conformation with a cis orientation of the nitrogen and oxygen atoms (θ = 0° or close to it) than for transoid conformations because of overlapping in the opposite phase. Judging from the literature data [10, 11], such carbonyl derivatives of azines exist in a transoid conformation that is favorable for orbital interaction with θ = 0-25°. Thus both interactions (n-σ* and n-π*) in this case are permitted. One must particularly note the important electronic consequences of this interaction, which reduce to transfer of electrons of the unshared pair to the carbonyl fragment and to a decrease, as a consequence of this, of the acceptor properties of the azine substituent.

A confirmation of the possibility of this sort of orbital interaction is the negative fractional order of the bond [12, 13] of the P_z orbital of the nitrogen atom with the carbon atom of the carbonyl group calculated by the CNDO/2 method.

The model of orbital interaction (Fig. 1a) finds further confirmation in an analysis of the tautomeric equilibrium of 3-pyridazinoyl- (VII) and 2-pyrimidoylacetic (VIII) esters. In the first case (Fig. 1b) one must take into account the interaction of two unshared pairs of adjacent nitrogen atoms, which leads to splitting of the energy levels. As a consequence of this, the energy of the upper occupied level increases (according to the data from photoelectronic spectroscopy [14], this splitting is ≈ 2 eV), which in turn leads to a decrease in the difference in the energies of the interacting orbitals. In addition, the pushing apart of the unshared pairs increases the overlapping of the orbital of the unshared pair with the orbitals of the C=O group. Both of these factors should lead to even greater stabilization of the keto form for 3-pyridazinoylacetic ester (VII) as compared with II, V, and VI, since, according to [15]

$$\Delta E_{12}^{ij} = \frac{2|H_{12}^{ij}|^2}{\Delta e_{12}}, \quad (3)$$

where E_{12}^{ij} is the energy of the two-electron orbital stabilization, H_{12}^{ij} is the matrix element of the interaction, which is proportional to the overlap interval, and Δe_{12} is the difference in the energies of the interacting levels. In fact, a comparison of the K_t values for 3-pyridoyl- (III) and 3-pyridazinoylacetic (VII) esters shows that for VII the introduction of an α-nitrogen atom not only does not increase the enol content but also gives rise to a substantial shift of the equilibrium to the opposite side (Table 1).

In the case of 2-pyrimidoylacetic ester it can be seen that the unshared pair of the second nitrogen atom ("cis" with respect to the oxygen atom) cannot effectively overlap with both the σ* and π* orbitals of the carbonyl group (Fig. 2) because of overlapping in opposite phases. As a consequence of this, one might expect that absence of the "anomalous" effect of the α heteroatom, i.e., on passing from 2-pyridoyl- (II) to 2-pyrimidoylacetic (VIII) ester the enol content should increase to a considerable extent. The experimental data show that this is actually true (Table 1).

Thus the data that we examined show that the introduction of β- and γ-nitrogen atoms leads to a substantial increase in the percentage of the enol form, which is in agreement with the conclusion drawn on the basis of the simple valence MO method. However, the effect of the introduction of a heteroatom in the α position depends substantially on the magnitude of the interaction of the unshared pair of the nitrogen atom with the closely located reaction center, viz., the carbonyl group. The examined type of interaction is possible for a large number of heterocyclic substituents that contain a heteroatom in the α position. The electronic effects of such substituents may depend substantially on the interaction between the electron pair of the heteroatom and the adjacent reaction center, which has a symmetrically suitable vacant orbital with a relatively low energy.

EXPERIMENTAL

Compounds II-VIII were synthesized in [1, 16]. Compound IX was synthesized by the method in [17] in 30% yield and had mp 108-110°C (mp 105-108°C [18]). PMR spectrum ($CDCl_3$, 3% concentration, 35°C), δ: 3.83 (s, CH_3, ketone), 3.89 (s, CH_3, enol), 4.11 (s, CH_2, ketone), 5.96 (s, CH, enol), 7.26 (m, 5-H), 7.86 (m, 3-H), and 9.56 ppm (m, 6-H). The tautomeric mixture contained 76% enol.

In the quantum-chemical calculations carried out at the Computer Center, Siberian Branch, Academy of Sciences of the USSR, we used programs provided by I. I. Zakharov.

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SYNTHESIS OF DERIVATIVES OF PYRAZOLO[3,4-d]PYRIMIDIN-3-YLACETIC ACID AND THEIR NUCLEOSIDES

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3-Cyanomethyl-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine was synthesized on the basis of 3-cyanomethyl-4-cyano-5-aminopyrazole. Ribosylation of this product gave 1-(2',3',5'-tri-O-acetyl-β-D-ribofuranosyl)-3-cyanomethyl-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine in 63% yield and small amounts of the 1-α and 2-β isomers. A number of derivatives of 6-methylmercaptopyrazolo[3,4-d]pyrimidin-3-ylacetic acid and their 1-ribosides were synthesized. The 4-methylmercapto group was replaced by amino, hydrazino, oxo, N-piperidino, and N-morpholino groups. The nitrile group was saponified in an alkaline medium to carbamoyl and carboxy groups. The corresponding 4-morpholino and 4-piperidino derivatives were obtained by the reaction of 3-cyano-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine per-O-acetylated 1-β-D-ribofuranoside with secondary cyclic amines. The high resistance of the 6-methylmercapto group to the action of nucleophilic agents and the higher reactivity of the 4-methylmercapto group as compared with the nitrile group are discussed. Data on the cytotoxic activity of the synthesized compounds were obtained.

The synthesis and chemical transformations of 3-cyano-4,6-dimethylmercaptopyrazolo-[3,4-d]pyrimidine and its 1-riboside, which we previously described in [1, 2], led to a number of compounds that have valuable biological properties. We demonstrated for the first time not only the cytotoxic activity but also the antivirus activity in this series of compounds [3]. High cytotoxic activity was also observed in the case of nucleosides of 4-monosubstituted and 3,4-disubstituted pyrazolo[3,4-d]pyrimidines; the introduction of a substituent in the 3 position led to intensification of the activity [4]. A further study of substituted pyrazolo[3,2-d]pyrimidines and their nucleosides seems of doubtless interest.

In the present paper we describe the synthesis of 3-cyanomethyl-4,6-dimethylmercaptopyrazolo[3,4-d]pyrimidine (IV) and its 1-riboside (VII), as well as their chemical transformations.

We obtained [3,4-d]pyrimidine IV from 3-cyanomethyl-4-cyano-5-aminopyrazole (I) by methods similar to those described in [1, 5]. It may be assumed that pyrazolothiazine II,

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