TAUTOMERISM OF AZINE DERIVATIVES.

6.* TAUTOMERISM OF 2-PYRIMIDINYLMETHANE DERIVATIVES

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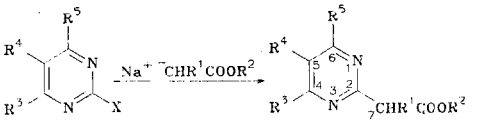
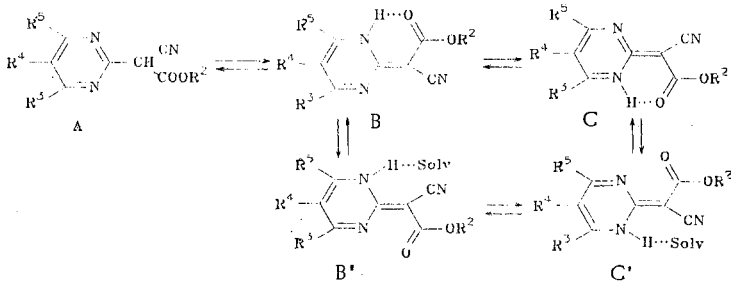
The existence of a pyrimidinyl—pyrimidinylidene tautomeric equilibrium in solutions of 2-pyrimidinylcyanoacetic acid esters in $CDCl_3$ was observed. Unsymmetrically substituted compounds form two types of ylidene tautomers that differ with respect to the position of the NH proton, the ratio between which is controlled by the substituents in the 4(6) position. The introduction of both donor and acceptor substituents into the 5 position of the pyrimidine ring increases the amount of the pyrimidine form. The same thing occurs when the polarity of the solvent is decreased. The addition of DMSO or DMF to $CDCl_3$ leads to conversion of the intrachelate ylidene tautomers to unchelated tautomers. Protonation (CF_3COOH) shifts the equilibrium to favor the ylidene tautomer that has higher basicity.

Previously among derivatives of 4-pyrimidinylmalonic and 4-pyrimidinylcyanoacetic acid esters and 4-pyrimidinylnitromethanes we found the first examples [2, 3] of a pyrimidinyl—pyrimidinylidene tautomeric equilibrium. Tautomerism of this type remains uninvestigated for 2-pyrimidinylmethane derivatives. The aim of the present research was to search for tautomeric compounds among 2-pyrimidinylmethane derivatives and to study their behavior in various solvents. For this, a number of 2-pyrimidinylmethane derivatives (I-XVI, Table 1) were obtained by condensation of halo- or methylsulfonylpyrimidines with cyanoacetic, malonic, methylsulfonylacetic, and phenylacetic acid esters.



I-XVI

Three principal tautomeric forms are possible for I-XVI: pyrimidine form A and two (in the case of unsymmetrical substitution) ylidene forms B and C. The formation of unchelated analogs of the ylidene tautomers, viz., B' and C', which are stabilized by an intermolecular hydrogen bond (HB) with the solvent, is also extremely probable in strongly basic solvents [dimethyl sulfoxide (DMSO) and hexamethylphosphoric triamide (HMPT)].



*See [1] for communication 5.

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TABLE 1. Synthetic Conditions and Properties of I-XVI

Compound	R^1	R^2	R^3	R^4	R^5	Synthetic conditions: temp., °C	Synthetic conditions: time, h	mp, °C	^{1}H chemical shifts, δ, ppm ($CDCl_3$, 40°C): form	CH	4-H	5-H	6-H	Yield, %
I	CN	C_2H_5	H	H	H	100	6	187—190	B	—	8,71	6,43	7,35	90
II	CN	C_2H_5	H	CH_3	H	100	4	217—219	B	—	8,6	—	7,62	80
III	CN	C_2H_5	H	C_6H_5	H	100	4	200—202	B	—	8,95	—	8,0	100
IV	CN	C_2H_5	H	Cl	H	70	3	198—206	A	5,09	8,72	—	8,72	100
									B	—	8,58	—	7,88	
V	CN	C_2H_5	H	Br	H	70	3	185—193	A	5,08	8,81	—	8,81	90
									B	—	8,60	—	7,90	
VI	CN	C_2H_5	H	*p*-NO_2—C_6H_4—	H	50	0,5	249—250	A	5,30	8,45	—	8,45	90
									B	—	8,64	—	7,41	
VII	CN	C_2H_5	H	OCH_3	H	90	1	176—185	A	5,03	8,27	—	8,27	40
									B	—	8,66	—	7,16	
VIII	CN	C_2H_5	H	$N(CH_3)_2$	H	110	2	184—190	A	5,00	8,26	—	8,26	45
									B	—	8,47	—	7,14	
IX	CN	C_2H_5	H	H	CH_3	100	4	139—143	B	—	8,52[a]		—	100
									C	—	7,75[b]	6,65[c]	—	
X	CN	C_2H_5	H	H	C_6H_5	80	8	183—184	B	—	7,57[a]	6,03[a]	—	60
XI	CN	C_2H_5	H	H	OCH_3	80	8	164—168	C	—	7,68[d]	6,02[e]	—	85
XII	CN	C_2H_5	OCH_3	H	OCH_3	80	2	184—186	C	—	—	5,38	—	80
XIII[f]	$COOCH_3$	CH_3	H	H	H	60	3	Oil	A	5,12	8,90	7,40	8,90	50
XIV[g]	$COOCH_3$	CH_3	H	H	C_6H_5	80	1,5	62—65	A	5,13	8,70	7,56	—	50
XV	CH_3SO_2	C_2H_5	C_6H_5	H	C_6H_5	80	1,5	143—150	A	5,12	—	—	—	60
XVI	C_6H_5	C_2H_5	C_6H_5	H	C_6H_5	80	1,5	111—113	A	5,14	—	7,96	—	70

[a]Doublet, J_{45} = 5 Hz. [b]Triplet, $J_{45} = J_{43}$ = 6 Hz. [c]The signals of the B and C forms are superimposed. [d]Triplet, $J_{43} = J_{45}$ = 7 Hz. [e]Doublet, J_{45} = 7 Hz. [f]^{13}C NMR spectrum in $CDCl_3$ (CF_3COOH), δ, ppm: C=O 166 (171.2), $C_{(2)}$ 162.9 (153.9), $C_{(4,6)}$ 157.3 (155.8), $C_{(5)}$ 119.8 (109.8), $C_{(7)}$ 61.2 (83.0), and CH_3 52.7 (53.6). [g]^{13}C NMR spectrum in $CDCl_3$ (CF_3COOH), δ, ppm: C=O 166.7 (171.7), $C_{(2)}$ 162.8 (153.2), $C_{(4)}$ 157.6 (158.3), $C_{(5)}$ 114.9 (106.8), $C_{(6)}$ 163.9 (154.8), $C_{(7)}$ 61.4 (82.1), and CH_3 53.5 (53.5).

We have established that the presence of a signal of a methylidyne proton near 5 ppm in the PMR spectra and the presence of a νC=O band of an unconjugated ester group at 1750 cm^{-1} in the IR spectra are characteristic for tautomers of the pyrimidine type A: A νC≡N band virtually does not appear in the IR spectra for the A form. The presence of a long-wave absorption maximum at 330-400 nm in the UV spectra, the presence of a signal of an NH proton at ~14 ppm in the PMR spectra, and the presence of an intense νCN band at ~2210 cm^{-1} and a νC=O band at ~1650-1680 cm^{-1} in the IR spectra are signs of ylidene forms B and C. Using these signs, in the case of 5-substituted 2-pyrimidinylcyanoacetic acid esters we have found the first instance of a pyrimidinyl-pyrimidinylidene tautomeric equilibrium among 2-pyrimidinylmethane derivatives (see [4] for our preliminary communication). Proton magnetic resonance spectroscopy makes it possible to reliably distinguish these forms and to determine the ratio of tautomers A, B, and C (Table 2).

The position of the equilibrium depends substantially on the type of R^4 substituent; the fact that the introduction of both electron-donor (VII and VIII) and electron-acceptor (IV-VI) substituents shifts the equilibrium to favor aromatic form A is unusual. In the case of VII and VIII the increase in the percentage of the A form is evidently associated with a decrease in the acidity of this tautomer (i.e., with an increase in the relative stability [5]) as a consequence of the strong electron-donor effect of the methoxy and dimethylamino groups (see [6]). However, the stability of tautomer B in this case hardly increases substantially, since an energetically unfavorable interaction of two π-donor groups [$N(CH_3)_2$ and NH] through a double bond arises in this form [7]. In the case of IV-VI the acidity of the A form is increased under the influence of substituents (see [6]); however, the acidity of tautomer B is increased (the stability is decreased) to an even greater extent, since the acidic center of the B form (the NH group) is closer to acidifying substituent R^4. Thus the shift of the equilibrium to favor tautomer A observed in the case of IV-VIII is evidently due to different factors. When R^4 = Cl, Br, and p-$NO_2C_6H_4$, the chief factor is destabilization of the tautomer of the B type; when R^4 = OCH_3 and $N(CH_3)_2$, the chief factor is stabilization of the tautomer of the A type.

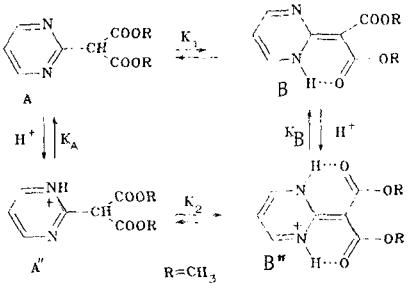
In an examination of the effect of α substituents (IX-XI), in analogy with 2-hydroxypyridines [8], one might have expected that the B form would be destabilized by substituents R^5 with a −I effect. There are two possibilities in this case: a shift of the equilibrium to favor the A form or a shift to favor the second ylidene form C with the NH group remote from the acidifying substituent. The experimental data show that the latter variant is realized, i.e., the introduction of an α substituent has an extremely substantial effect on the equilibrium between the ylidene tautomers.

In contrast to the previously investigated 4-pyrimidinylmalonic esters [2], 2-pyrimidinylmalonic acid esters XIII and XIV, as well as XV and XVI, do not display tautomeric properties and exist in aromatic form A in solutions in $CHCl_3$ or CCl_4. Evidence for this is provided by the absence in their UV spectra of the long-wave maximum (~330-400 nm) that is characteristic for tautomers of the ylidene type (B and C).

Since it is known that the position of a tautomeric equilibrium may depend markedly on the properties of the medium, we studied the behavior of 2-pyrimidinylmethanes in varous solvents, including solvents with basic and acidic character. We found that a decrease in the polarity of the medium increases the percentage of the aromatic form. For example, according to UV spectroscopic data, on passing from a solution of IV in $CHCl_3$ to a solution in heptane–$CHCl_3$ (49:1) the amount of the A form increases from 9% to 50%. Destabilization of the ylidene forms on passing to low-polarity solvents was also previously observed for other types of azinylidene equilibria [8].

There has been a report [9] in which the development of an unchelated NH tautomer of the B' type is noted for 2-pyridylcyanoacetic ester in $CHCl_3$. We have noted the development of unchelated tautomers B' and C' for esters IX and X only in the presence of strongly basic solvents that are capable of forming a strong hydrogen bond with the NH group. The following observations constitute evidence in favor of the formation of unchelated forms. When dimethyl sulfoxide is added to solutions of IX or X in $CHCl_3$, a 2-4 ppm shift to strong field of the signal of the carbonyl carbon atom occurs in the ^{13}C NMR spectrum. This change is a characteristic sign of disruption of the chelate ring due to the formation of an intermolecular hydrogen bond with basic solvents [10]. In addition, for IX and X the presence of DMSO and DMF gives rise to an appreciable shift of the tautomeric equilibrium to favor the C' form. This is readily explained by the fact that the less sterically shielded NH group proves to be more accessible for solvation by the solvent in the case of cleavage of the intramolecular bond. An increase in the amount of DMSO to 100% is accompanied by appreciable (and sometimes complete) ionization of 2-pyrimidinylcyanoacetic acid esters; this is clearly apparent when one compares the UV spectra of the compounds in DMSO with the spectra of their sodium salts.

Among the factors that affect the tautomeric equilibria of heterocycles, the effect of strongly acidic solvents [11, 12] that are capable of protonating I-XVI, which have rather high basicities (pK_a = 1.3 for pyrimidine), may be particularly important. We therefore studied the behavior of XIII and XIV, which in neutral solvents of the $CHCl_3$ type exist in the A form and do not display tautomeric properties in the presence of trifluoroacetic acid, the acidity of which (H_0 = 3.03) ensures monoprotonation of pyrimidine derivatives [13].



When trifluoroacetic acid is added to solutions of XIII and XIV in chloroform, a characteristic maximum at 330-400 nm, which evidently constitutes evidence for a marked shift of the equilibrium to favor the ylidene form, appears in the UV spectrum. For rigorous proof of this we used the characteristic signs of the development of cations of the A" and B" type that were previously found in a study of the corresponding cations of pyridyl- and pyrimidinylcyanoacetic acid esters [12]. A signal of a CH proton (form A) between 5 and 6 ppm is absent in the PMR spectra of XIII and XIV in CF_3COOH. Instead of a $C_{(7)}$ signal of the

TABLE 2. Amounts of the Tautomeric Forms (%) for I-XVI from PMR Spectroscopic Data ($CDCl_3$, 40°C, ~1% solutions)

Compound	Form		Compound	Form	
	A	B(C)		A	B(C)
I	Traces	100	IX	—	100[a]
II	Traces	100	X	2	98[b]
III	—	100	XI	—	100[c]
IV	9	91	XII	—	100
V	5	95	XIII	100	—
VI	20	80	XIV	100	—
VII	35	65	XV	100	—
VIII	40	60	XVI	100	—

[a]The B:C ratio was 50:50. [b]The B:C ratio was 28:70. [c]Only tautomer C.

aromatic tautomer (60 ppm, $CDCl_3$), a $C_{(7)}$ signal at ~80 ppm appears in the ^{13}C NMR spectra in trifluoroacetic acid. The monoresonance spectrum shows that this signal cannot be the signal of the aromatic tautomer (a direct $^1J_{^{13}C-H}$ spin–spin coupling constant is absent) but corresponds to a tautomer of the ylidene type. A comparison of the positions of the signals of the ring $C_{(4)}$, $C_{(5)}$, and $C_{(6)}$ atoms of esters XIII and XIV (Table 1) with the analogous signals in the spectra of the cations of pyrimidinylcyanoacetic acid esters [12] also confirms the development of a protonated ylidene form.

Thus the ^1H and ^{13}C NMR spectra are in agreement with the UV spectroscopic data and constitute evidence for a virtually complete shift of the equilibrium in a solution of acid to favor the ylidene tautomer. It follows from our previously obtained [11]* expression $K_2 = K_1(K_B/K_A)$ (where K_2 and K_1 are the constants of the tautomeric equilibrium of the protonated and unprotonated forms, and K_A and K_B are the basicity constants of the starting tautomers) that such a pronounced change in the position of the equilibrium is associated with the higher basicity of ylidene tautomeric form B as compared with the aromatic form. It must be noted that for XVI passing to CF_3COOH solutions does not lead to the development of an ylidene tautomer. This is evidently associated with a decrease in the number of acceptor substituents attached to the CH fragment, which, as is well known, markedly decreases the relative stability of the ylidene forms [3].

Thus the position of the tautomeric equilibrium of 2-pyrimidinylmethanes depends to a substantial degree on the substituents in the heterocyclic part of the molecule and attached to the CH fragment, as well as on the solvent used. Whereas strongly basic solvents give rise to the formation of the p-quinoid NH form in the case of the 4-pyrimidinyl derivatives, the development of unchelated ylidene tautomers is characteristic for the 2-pyrimidinyl derivatives. Ionization is observed for both the 2- and 4-pyrimidinyl methanes when the basicity is increased.

One of the strongest factors that affect the position of the tautomeric equilibrium is protonation, which favors the ylidene tautomer.

EXPERIMENTAL

The IR spectra were recorded with a UR-20 spectrometer. The UV spectra were obtained with a Specord UV-vis spectrophotometer. The ^1H and ^{13}C NMR spectra were obtained with a Bruker WP-80 spectrometer under pulse conditions with accumulation of the signals. The ratios of the tautomers were determined from the integral intensities of the signals of the ring protons. To increase the accuracy of integration 10-100 scans were made with a 10-20-sec lag between pulses, which substantially exceeded the relaxation time of the protons. 2-Pyrimidinylmethanes I-XVI were obtained by the reaction of the corresponding fluoro- (XV), chloro- (I-XII, XIV, and XVI), and methylsulfonylpyrimidines (XIII) with a threefold excess of sodium derivatives of substituted acetic acid esters in analogy with [2]. The individuality of the chromatographically purified and recrystallized compounds was monitored by thin-layer chroma-

*An error was printed in [11] in the scheme that illustrates the tautomeric equilibrium of β-keto esters with the participation of protonated forms: the —OH and —CH_2— groups should be depicted instead of —O^- and —CH—.

tography (TLC) (Silufol UV-254) and PMR spectroscopy; all of the compounds gave satisfactory results of analysis for carbon, hydrogen, and nitrogen. Compounds I-III, VIII, XII, and XV were recrystallized from alcohol, IV, V, VII, and XI were recrystallized from benzene, VI was recrystallized from alcohol–DMF, IX and X were recrystallized from benzene–CCl_4, XIV was recrystallized from aqueous alcohol, and XVI was recrystallized from CCl_4. The melting points of the tautomeric compounds were not constant and depended on the rate of melting, the peculiarities of crystallization, etc.

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TAUTOMERISM OF AZINE DERIVATIVES.

7.* THERMODYNAMIC PARAMETERS OF THE 1,3-PROTOTROPIC TAUTOMERIC EQUILIBRIUM OF AZAHETARYLMETHANES

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The constants of the hetaryl–ylidene tautomeric equilibrium in $CDCl_3$ over a wide range of temperatures were measured for azinylmalonic and azinylcyanoacetic acid esters. High-temperature sensitivity of the position of the equilibrium for 2-pyrimidinylcyanoacetic acid esters was demonstrated. The differences in the ΔS values of the equilibrium for derivatives of malonic and cyanoacetic acid esters were explained by different freedoms of rotation about the exocyclic C–C bond in the aromatic tautomeric form.

In the course of a systematic study of the tautomerism of azines we have determined for the first time the thermodynamic characteristics of the prototropic equilibrium of the A $\rightleftarrows$ B type in the azahetarylmethane series. We used ethyl 5-methoxy-2-pyrimidinylcyanoacetate (I), ethyl 5-dimethylamino-2-pyrimidinyl cyanoacetate (II), dimethyl 2-methyl-4-pyrimidinylmalonate (III), dimethyl 3-pyridazinylmalonate (IV), and ethyl 6-methoxy-3-pyridazinylcyanoacetate (V) as models. Comparable amounts of tautomeric forms A and B are observed for I-V from PMR

*See [1] for communication 6.

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