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The tautomerism of 1,4-diazepines fused with pyrimidine rings was studied by means of nmr spectroscopy, X-ray analysis and quantum chemical calculations. It was found that in the case of 6,8-diphenylpyrimido[4,5-*b*][1,4]diazepin-4-ols (**7a** - **e**) the enamine form is more stable than the diimine form. This result is rationalized with the electron-withdrawing effect of the 4-hydroxypyrimidine ring and with the formation of intermolecular hydrogen bonds. In contrast to **7a** – **e**, the 6,8-diaryl-2,3,4,7-tetrahydro-1,3-dimethyl-1*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4-diones (**9a**, **c**, **f**) exist in the diimine form.

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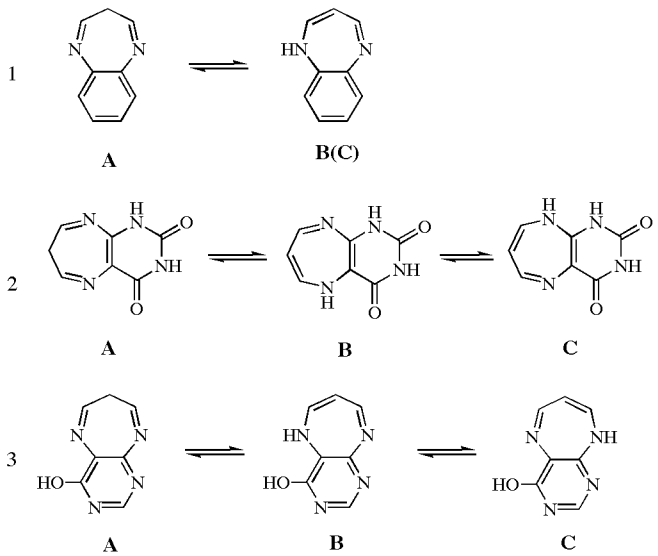
In continuation of our investigation on nitrogen-containing seven-membered heterocycles [1-4] we studied the tautomerism of 1,4-diazepines fused with pyrimidine rings. The interest in these compounds is based on their biological and pharmacological properties; thus, a series of publications on pyrimido[4,5-*b*][1,4]diazepines appeared recently [5-12].

It is known that fused 1,4-diazepines like **1**-**3** can exist in several tautomeric forms **A – C** (Scheme 1). On the basis of literature data [13-16] for benzoanellated 1,4-diazepines it could be assumed that the enamine forms **B** and **C** are metastable whereas the nonconjugated form **A** should predominate. It is also known [17] that electron-acceptors (*e.g.* NO_2 groups) introduced in the six- or seven-membered ring of 1,5-benzodiazepines can stabilize the enamine tautomers. In our opinion an electron acceptor such as the pyrimidine ring should decrease the electron density in the seven-membered ring and therefore stabilize the tautomeric form **B** or **C**. In this context we studied the influence of pyrimidine rings fused with diazepine rings on the imine-enamine equilibrium (**ABC**).

Scheme 1



We undertook *ab initio* (HF 6-31G**) quantum chemical calculations of the thermodynamic properties of the model compounds shown in Scheme 1. The influence of the solvent in these calculations was taken into account in the frame of the polarizable continuum model (PCM) [18]. The results of the quantum chemical calculations are summarized in Table 1.

Table 1

Difference of Gibbs Energies (ΔΔG) between Tautomer **A** and Tautomer **B** or **C** of the Fused Diazepines **1** – **3** (calculated with *ab initio* HF 6-31G**)

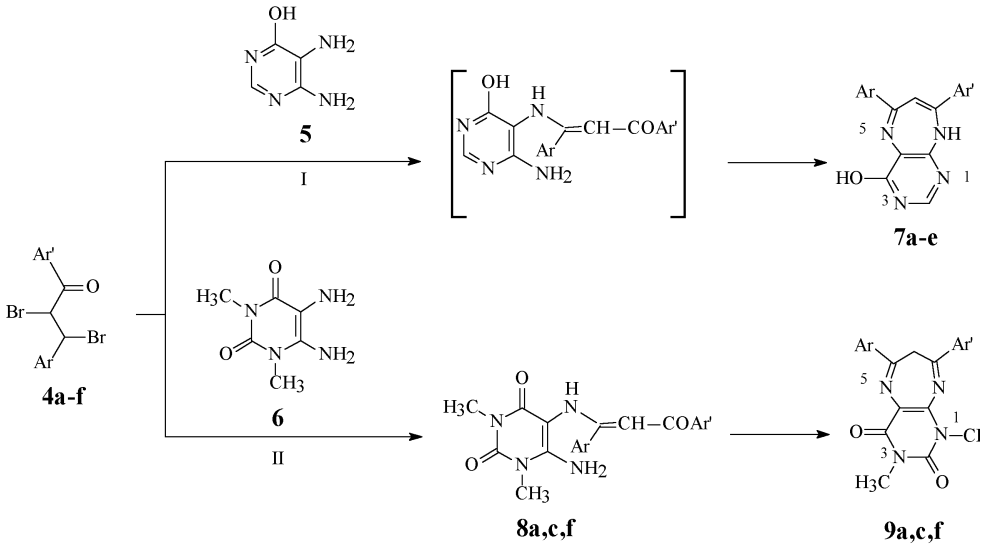
Compound	Medium	$\Delta\Delta G = \Delta G_{B/C} - \Delta G_A$ [kcal/mol] Form **B**	Form **C**
1	Gas phase	4.36	
	Dimethyl sulfoxide	3.92	
	Chloroform	4.13	
2	Gas phase	-0.35	9.74
	Dimethyl sulfoxide	4.55	5.16
	Chloroform	2.85	8.03
3	Gas phase	2.57	2.76
	Dimethyl sulfoxide	4.52	-0.84
	Chloroform	3.86	-1.70

In the case of the benzodiazepine **1**, the diimine form **A** is more stable than form **B**/**C** by ΔΔG of 3.9 – 4.4 kcal/mol. The situation can be reversed for the pyrimidodiazepines **2** and **3**. The enamine form **C** of compound **3** is the most stable tautomer in dimethyl sulfoxide and chloroform. It is important to note that the PCM model does not involve any specific interactions between the compounds and the solvent, for example hydrogen bonding O....H.

Such interactions could lead to an additional decrease of the energy of the enamine forms in the compounds **1** - **3**.The 6,8-diaryl-9*H*-pyrimido[4,5-*b*][1,4]diazepin-4-ols **7a** - **e** were prepared by the reaction of the α,β-dibromoketones **4a** - **e** with 5,6-diamino-4-hydroxypyrimidine **5** in methanol in the presence of triethylamine (Scheme 2, reaction I). The analogous reaction of **4a**, **c**, **f** with the pyrimidine derivative **6** led to the Michael adducts **8a**, **c**, **f**, which were subsequently cyclized to the corresponding 6,8-diaryl-2,3,4,7-tetrahydro-1,3-dimethyl-1*H*-pyrimido[4,5-*b*][1,4]-diazepine-2,4-diones (**9a**, **c**, **f**) by acid catalysis (Scheme 2, reaction II).

The ^{1}H nmr spectra of **7a** – **7e** do not contain any signals related to methylene groups; instead they exhibit broad singlets for NH protons which are superimposed at δ = 8.03 ± 0.01 by the singlets of the OH groups on C-4. The resonance signals of **7** and **9** is due to the AB spin pattern obtained for **9a**, **c**, **f**. The diastereotopic geminal protons on C-7 reveal at room temperature a slow inversion of the diazepine rings in terms of the nmr time scale. The big difference $\delta(H_B)$ - $\delta(H_A) \approx 4$ ppm results from the fact that H_A is shielded by the aryl groups on C-6 and C-8 whereas H_B is deshielded. In 1,5-benzodiazepines the ring inversion becomes slow below –60 °C [19].

Scheme 2



4, 7, 8, 9	a	b	c	d	e	f
Ar	C_6H_5	C_6H_5	C_6H_5	4-F-C_6H_4	4-Cl-C_6H_4	4-C_6H_5-C_6H_4
Ar'	C_6H_5	4-Cl-C_6H_4	4-Br-C_6H_4	C_6H_5	C_6H_5	C_6H_5

Table 2

^{1}H nmr Spectra of the Compounds **7a** - **e** and **9a**, **c**, **f** (δ Values in DMSO-d_6 as a Solvent and TMS as Internal Standard)

Compound	H_2C-7 H_A	H_B	^2J [Hz]	HC-7 s	ArH, Ar'H and NH, OH [a], m	2-H br s	CH_3, s
7a	-		-	6.12	7.22 - 7.90	8.02	-
7b	-		-	6.13	7.35 - 7.80	8.03	-
7c	-		-	6.10	7.40 - 7.88	8.02	-
7d	-		-	6.18	7.10 – 7.88	8.04	-
7e	-		-	6.16	7.16 - 7.90	8.03	-
9a	2.03	5.91	-11.5	-	7.30 – 8.20	-	3.31, 3.42
9c	2.04	5.92	-11.3	-	7.30 - 8.20	-	3.31, 3.43
9f	2.08	5.99	-11.5	-	7.30 - 8.30	-	3.31, 3.45

[a] Superimposed.

The ^{1}H nmr data of **7a** - **e** and **9a**, **c**, **f** are listed in Table 2. The most characteristic difference between the ^{13}C nmr signals of **7a** – **e** are listed in Table 3. The ir spectra of **7a** – **7e** provide a further proof for hydrogen bonds.

Table 3

^{13}C nmr Data of the Compounds **7a** - **e** (δ Values in DMSO-d_6 as a Solvent and TMS as Internal Standard)

	C-4*a*	C-7	*p*-C_{Ar}	*p*-C_{Ar}'	*o*-C_{Ar}, *m*-C_{Ar}, *o*-C_{Ar}', *m*-C_{Ar}'	*i*-C_{Ar}	*i*-C_{Ar}'	C-2	C-6	C-4, 8, 9*a*
7a	108.5	113.8	128.2	130.3	129.4, 128.5, 128.7, 128.4	133.2	136.2	156.6	143.3	156.1, 157.2, 159.9
7b	108.5	113.9	128.2	[a]	129.5, 128.5, 130.6, 129.5	133.2	134.9	156.8	143.0	156.0, 156.2, 159.9
7c	108.5	113.9	128.2	123.7	129.5, 128.5, 131.4, 130.8	133.2	135.3	156.8	142.9	156.1, 156.2, 159.9
7d	108.5	112.7	159.9	130.3	131.5, 115.5, 128.7, 128.4	129.8	136.1	156.7	143.0	156.1, 157.1, 159.9
7e	108.5	112.3	132.4	130.3	131.0, 128.7, 128.5, 128.4	132.2	136.0	156.7	143.7	156.0, 156.9, 160.0

[a] Superimposed.

Thus, the analysis of the nmr data obtained shows that the 6,8-diaryl-2,3,4,7-tetrahydro-1,3-dimethyl-1*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4-diones **9a**, **c**, **f** exist in DMSO solution in the tautomeric diimine form **A**. In contrast the 6,8-diaryl-4-hydroxy-9*H*-pyrimido[4,5-*b*]-[1,4]diazepines **7a** - **e** have enamine structures (**B**/**C**). Although the spectral characteristics of the compounds **7a** - **e** agree principally with both **B** and **C**, we assume - according to the quantum chemical calculations (Table 1) - the realization of the 9*H* structure **C**.

The stabilisation of the enamine tautomer of **7a** - **e** compared to the imine form can be explained by several reasons. First of all, the condensation of the diazepine ring with the pyrimidine ring leads to a decrease of electron density in the seven-membered ring. An influence of different electron-acceptors on the tautomeric equilibrium of benzoanellated diazepines was described in the literature [17]. An additional stabilization of the enamine form of **7a** - **e** may be given by solvation effects (See Table 1).An X-ray diffraction study established that compound **9a** is also present in the crystal state in the diimine form. Figure 1 shows a perspective view of molecule **9a**. Selected bond lengths and angles are listed in Table 4. The conformation of the diazepine ring can be described as a "boat". (The atoms $N_{(3)}$, $N_{(4)}$, $C_{(4)}$ and $C_{(6)}$ are placed in the same plane, from which the atoms $C_{(3)}$, $C_{(5)}$ and $C_{(7)}$ deviate by -0.62, -0.78 and -0.62 Å respectively). The uracil ring is almost planar with small deviations [-0.06 Å of $C_{(1)}$ and $N_{(2)}$] from the plane of the remaining ring atoms $N_{(1)}$, $C_{(2)}$, $C_{(3)}$ and $C_{(7)}$. Evidently, both N(3) – C(4) and N(4) – C(6) bond lengths have almost the same value of 1.29 Å (Table 4) which is compatible with π-imine bonds.

Table 4

Selected Bond Lengths [Å] and Angles (°) in Compound **9a**

$N_{(1)}$-$C_{(1)}$	1.387(2)	$O_{(1)}$-$C_{(1)}$-$C_{(7)}$	123.9(2)
$N_{(1)}$-$C_{(2)}$	1.389(3)	$N_{(1)}$-$C_{(1)}$-$C_{(7)}$	115.9(2)
$N_{(1)}$-$C_{(8)}$	1.468(3)	$O_{(2)}$-$C_{(2)}$-$N_{(2)}$	122.7(2)
$N_{(2)}$-$C_{(2)}$	1.373(2)	$O_{(2)}$-$C_{(2)}$-$N_{(1)}$	121.2(2)
$N_{(2)}$-$C_{(3)}$	1.392(2)	$N_{(2)}$-$C_{(2)}$-$N_{(1)}$	116.1.(2)
$N_{(2)}$-$C_{(9)}$	1.471(3)	$N_{(3)}$-$C_{(3)}$-$C_{(7)}$	125.7(2)
$N_{(3)}$-$C_{(4)}$	1.296(2)	$N_{(3)}$-$C_{(3)}$-$N_{(2)}$	113.5(2)
$N_{(3)}$-$C_{(3)}$	1.372(2)	$C_{(7)}$-$C_{(3)}$-$N_{(2)}$	120.2(2)
$N_{(4)}$-$C_{(6)}$	1.290(2)	$N_{(3)}$-$C_{(4)}$-$C_{(10)}$	117.2(2)
$N_{(4)}$-$C_{(7)}$	1.385(2)	$N_{(3)}$-$C_{(4)}$-$C_{(5)}$	120.7(2)
$O_{(1)}$-$C_{(1)}$	1.224(2)	$C_{(10)}$-$C_{(4)}$-$C_{(5)}$	121.5(2)
$O_{(2)}$-$C_{(2)}$	1.218(2)	$C_{(4)}$-$C_{(5)}$-$C_{(6)}$	104.2(2)
$C_{(1)}$-$C_{(7)}$	1.464(3)	$N_{(4)}$-$C_{(6)}$-$C_{(16)}$	119.2(2)
$C_{(3)}$-$C_{(7)}$	1.380(3)	$N_{(4)}$-$C_{(6)}$-$C_{(5)}$	119.9(2)
$C_{(4)}$-$C_{(10)}$	1.478(3)	$C_{(16)}$-$C_{(6)}$-$C_{(5)}$	120.9(2)
$C_{(4)}$-$C_{(5)}$	1.501(3)	$C_{(3)}$-$C_{(7)}$-$N_{(4)}$	125.7(2)
$C_{(5)}$-$C_{(6)}$	1.518(3)	$C_{(3)}$-$C_{(7)}$-$C_{(1)}$	119.2(2)
$C_{(6)}$-$C_{(16)}$	1.479(3)	$N_{(4)}$-$C_{(7)}$-$C_{(1)}$	114.6(2)
		$C_{(15)}$-$C_{(10)}$-$C_{(4)}$	122.2(2)
$C_{(1)}$-$N_{(1)}$-$C_{(2)}$	125.2(2)	$C_{(11)}$-$C_{(10)}$-$C_{(4)}$	119.8(2)
$C_{(1)}$-$N_{(1)}$-$C_{(8)}$	117.6(2)	$C_{(21)}$-$C_{(16)}$-$C_{(6)}$	119.4(2)
$C_{(2)}$-$N_{(1)}$-$C_{(8)}$	117.2(2)	$C_{(17)}$-$C_{(16)}$-$C_{(6)}$	122.0(2)
$C_{(2)}$-$N_{(2)}$-$C_{(3)}$	122.9(2)	$C_{(18)}$-$C_{(17)}$-$C_{(16)}$	120.2(2)
$C_{(2)}$-$N_{(2)}$-$C_{(9)}$	116.8(2)	$C_{(19)}$-$C_{(18)}$-$C_{(17)}$	120.9(3)
$C_{(3)}$-$N_{(2)}$-$C_{(9)}$	120.2(2)	$C_{(18)}$-$C_{(19)}$-$C_{(20)}$	119.9(2)
$C_{(4)}$-$N_{(3)}$-$C_{(3)}$	121.1(2)	$C_{(19)}$-$C_{(20)}$-$C_{(21)}$	120.0(3)
$C_{(6)}$-$N_{(4)}$-$C_{(7)}$	121.6(2)	$C_{(16)}$-$C_{(21)}$-$C_{(20)}$	120.3(2)
$O_{(1)}$-$C_{(1)}$-$N_{(1)}$	120.2(2)		

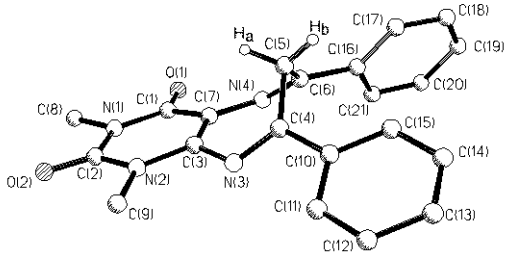


Figure 1. Molecular Structure of Compound **9a** in the Crystalline State.

Conclusion.

Different pyrimidine ring systems in **7a** – **e** and **9a**, **c**, **f** lead to different tautomeric structures of the condensed diazepine rings. The structural assignment based on nmr measurements is in accordance with *ab initio* calculations and an X-ray crystal structure analysis.

EXPERIMENTAL

The melting points were determined on a Kofler apparatus and were not corrected. The ^{1}H and ^{13}C nmr spectra were obtained on a Bruker AM 400 and on a Varian Mercury VX 200 in DMSO-d_6 with tetramethylsilane as internal standard.

The preparation of the 6,8-diaryl-9*H*-pyrimido[4,5-*b*][1,4]-diazepin-4-ols **7a**, **e** and their mass spectra are described in the literature [4].

General Procedure for the Preparation of Compounds **7b** – **d**.

To a solution of 0.34 g (2.7 mmoles) of commercially available 4-hydroxy-5,6-diaminopyrimidine (**5**) in 40 ml of methanol were added 2.7 mmoles of the ketones **4b** - **d** and 2 ml of triethylamine. The mixture was refluxed for 2 hours. The methanol was evaporated under reduced pressure. The precipitate formed was collected by filtration and washed with hot water. Recrystallisation from methanol led to the analytically pure products **7b** – **d**; their ^{1}H and ^{13}C nmr spectral data are listed in Tables 2 and 3, respectively.

8-(4-Chlorophenyl)-6-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepin-4-ol (**7b**).

This compound was obtained in a yield of 50 %, mp 258 – 260 °C. The ei ms (70 eV) spectrum showed peaks at m/z (%) 350/348 (100, M^+), 313 (38), 225 (27).

Anal. Calcd. for $C_{19}H_{13}ClN_4O$: C, 65.43; H, 3.76; N, 16.06. Found: C, 65.45; H, 3.90; N, 16.31.

8-(4-Bromophenyl)-6-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepin-4-ol (**7c**).

This compound was obtained in a yield of 48 %, mp 259 - 261 °C. The ei ms (70 eV) spectrum showed peaks at m/z (%) 394/392 (100, M^+), 313 (42), 269 (19), 189 (37).

Anal. Calcd. for $C_{19}H_{13}BrN_4O$: C, 58.03; H, 3.33; N, 14.25. Found: C, 58.10; H, 3.55; N, 14.36.

6-(4-Fluorophenyl)-8-phenyl-9*H*-pyrimido[4,5-*b*][1,4]diazepin-4-ol (**7d**).

This compound was obtained in a yield of 45 %, mp 290 – 291 °C. The ei ms (70 eV) spectrum showed peaks at m/z (%) 332 (100), 209 (19).

Anal. Calcd. for $C_{19}H_{13}FN_4O$: C, 68.67; H, 3.94; N, 16.86. Found: C, 68.61; H, 3.99; N 16.95.

The general procedures for the preparation of the 6-amino-1,3-dimethyl-5-(3-oxo-1,3-diaryl-1-propenylamino)-1,2,3,4-tetrahydropyrimidine-2,4-diones **8a**, **c**, **f,** the respective 6,8-diaryl-2,3,4,7-tetrahydro-1,3-dimethyl-1*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4-diones **9a**, **c**, **f** and their mass spectra are described in the literature [2]. The ^{1}H nmr spectra of **9a**, **c**, **f** are listed in Table 2. For 8-(4-bromophenyl)-2,3,4,7-tetrahydro-1,3-dimethyl-6-phenyl-1*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4-dione (**9c**), the following ^{13}C nmr signals were found in DMSO-d_6 : δ 28.1, 30.0 (CH_3), 37.2 (CH_2), 128.5, 128.7, 131.2, 131.9 (*o,m*-C_{Ar}, *o,m*-$C_{Ar'}$), 130.7 (*p*-C_{Ar}), 116.5 (C-4*a*), 126.5 (*p*-$C_{Ar'}$), 133.2, 135.0 (*i*-C_{Ar}, *i*-$C_{Ar'}$), 141.9, 143.6, 148.0, 149.9, 160.5 (C-2, C-4, C-6, C-8, C-9*a*).

Crystal Structure Analysis of 2,3,4,7-Tetrahydro-1,3-dimethyl-6,8-diphenyl-1*H*-pyrimido[4,5-*b*][1,4]diazepine-2,4-dione (**9a**).

The crystals of **9a** ($C_{21}H_{18}N_4O_2$) are monoclinic. At 293K was found a = 11.358(2), b = 9.435(2), c = 17.502(4) Å, β = 104.12(3), V = 1818.9(6) Å^3, space group $P2_1/c$, Z = 4, d_{calc} = 1.309 g/cm^3. Parameters of unit cell and intensity of 3691 reflections were measured on an automatic difractometer *Enraf-nonius CAD-4* (λ MoK_α radiation, graphite monochromator, θ/2θ scanning, $2\theta_{max}$ = 45°). The data obtained were refined with Blessing's programme [21].

The structure was solved by direct method using SHELXTL PLUS [22] package. Positions of the hydrogen atoms were located from electron density maps. The structure was refined by full-matrix least-square method against F^2 within anisotropic (H atoms within isotropic) approximation using 3128 reflections and was converted to wR_2 = 0.120 (R_1 = 0.043 for 2140 reflections with $F > 4\sigma(F)$, S = 1.03).

Crystallographic data for the structural analysis of **9a** have been deposited at CCDC depository No. 195039.

Quantum Chemical Calculations.

All *ab initio* quantum chemical calculations were carried out with the GAMESS [18] programme.

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