STRUCTURE DETERMINATION OF 3-(2,2-DISUBSTITUTED ETHENYL)AMINO- SUBSTITUTED HETEROCYCLIC SYSTEMS†

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†This paper is dedicated to the late Professor Drago Kolar

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Abstract

Two structural issues, orientation on enamino double bond and relative positions of substituents on 3-amino group, on a series of 3-(2,2-disubstituted ethenyl)amino-substituted heterocycles, such as 4*H*-pyrido-[1,2-*a*]pyrimidin-4-ones **3**, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **4**, 4*H*-pyrido[1,2-*a*]pyridin-4-ones **5**, 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones **6** and 2*H*-1-benzopyran-2-ones **7**, were resolved using basic ^{1}H NMR experiments.

Introduction

Recently, a series of 3-(2,2-disubstituted ethenyl)amino- substituted heterocycles such as 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones **3**, 5*H*-thiazolo[3,2-*a*]pyrimidin-5-ones **4**, 4*H*-pyrido[1,2-*a*]pyridin-4-ones **5**, 5,6,7,8-tetrahydro-2*H*-1-benzopyran-2-ones **6** and 2*H*-1-benzopyran-2-ones **7**, were prepared from the corresponding alkyl 2-[2,2-disubstituted ethenyl]amino-3-dimethylaminopropenoates **2** (*Scheme*).[1-7] As a part of this project, we now present a detailed study of structure of these compounds in the DMSO-d $_6$ solution.

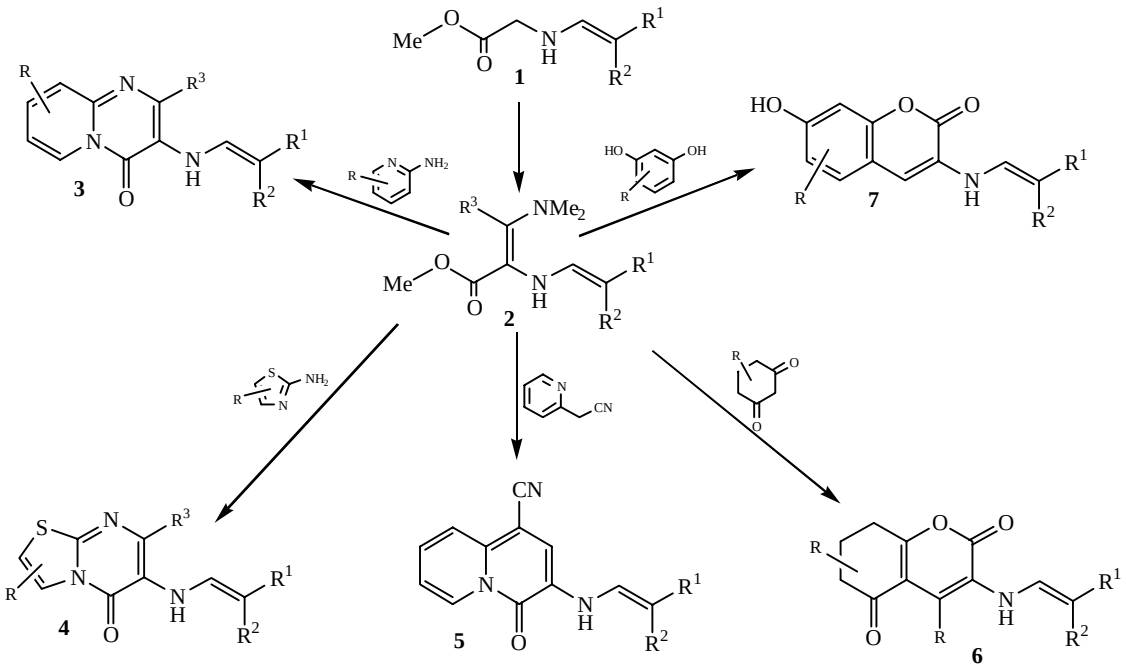
Results and discussion

We encountered two structural issues regarding these compounds which had to be resolved: orientation on enamine double bond and relative positions of substituents on 3-amino group, and tried to solve them by the means of ^{1}H NMR spectroscopy.

The first issue was addressed in two ways: 1.) signals were characterized on the basis of the *NH* shift, since it depends significantly on the group which is located *syn*

relative to the *NH* group (data for the δ_{NH} correlated to the R_{syn} group is summarized in *Table 1*). Since the coupling constants for NHCH group indicate the *anti* orientation in NHCH fragment (*J*=12.2-15.0Hz), this method allows unambiguous determination of geometric isomers when R^1 and R^2 groups are COOR and COR, while in the case of R^2 = CN, determination is not always possible.

Scheme. The synthesis of 3-(2,2-disubstituted ethenyl)amino- substituted heterocycles

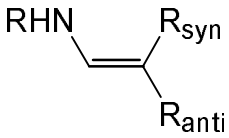


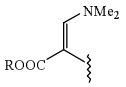
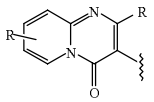
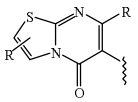
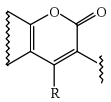
R^1,R^2= COOMe, COOEt, COOBn, COMe, CN; R^3= H, Me; R=H, Me,Cl, Br,OH;

2.) Second method is based on the comparison of the experimental and calculated chemical shift of the olefinic proton. Shifts were calculated using standard equation for trisubstituted olefins: $\delta_H = 5.25+Z_{gem}+Z_{cis}+Z_{trans}$ (relevant NMR data is assembled in *Tables 2* and *3*). Since our heteroarylamino group is not found in tables,[13] we had to extract the Z_{gem} value from experimental data of compounds with identical R^1 and R^2 groups and compounds where isomers could be unambiguously determined with first method.

We found that Z_{gem} value for 3-(4*H*-pyrido[1,2-*a*]pyrimidin-4-one)-ylamino group is Z_{gem} = 1.43 ppm and for 3-(2*H*-1-benzopyran-2-one)-ylamino group Z_{gem}= 1.21 ppm (*Table 3*). Thus calculated shifts for olefinic proton are in good agreement with experimental data (±0.05 ppm) for compounds where R^1 and R^2 is COOR or COMe.

Table 1. Chemical shifts of the NH group (δ ppm) correlated to the R_{syn} group, recorded in DMSO-d_6

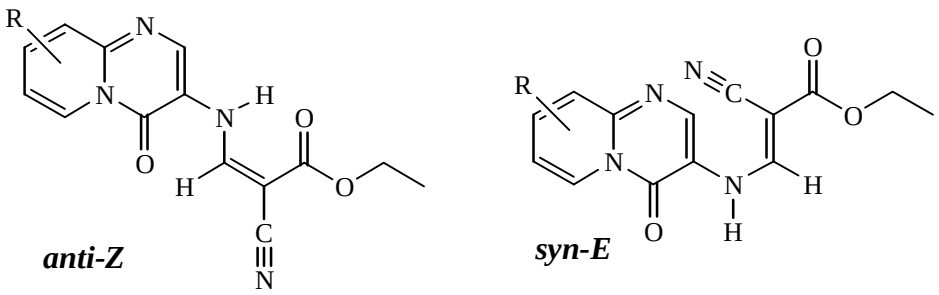


R	R_{syn}		
	CN	COOR	COR
	8.60 - 8.70	9.10 – 9.15	10.70 – 10.85
	9.20 – 9.30	9.50 – 9.80	11.40 – 11.60
	10.30 – 10.45	10.85 – 10.87	12.50 – 12.70
	10.30 – 10.45	10.40 – 10.70	12.40 – 12.55
	10.30 – 10.35	10.30 – 10.75	12.45 – 12.55

Compounds where R^1 = CN group, show two different types of signals for the *CHNH* structural element. Namely, major isomer of compound **3** show doublet (*J*=13-14 Hz) for *NH* between 10.85 and 10.87 ppm, and minor isomer singlet in 10.30-10.45 ppm interval.[7] We assumed that majority of compounds exist in *Z* form with *anti* orientation of *CHNH* element and minority in *E* form with *syn* orientation of *CHNH* element. A group of Japanese scientists encountered the same phenomenon while studying the synthesis and

structures of alkyl *N*-(2-pyridyl)aminomethylenecyanoacetates.[8] The structures of compound **3**, where R^1 = CN and R^2= COOEt are presented in *Figure 1*.

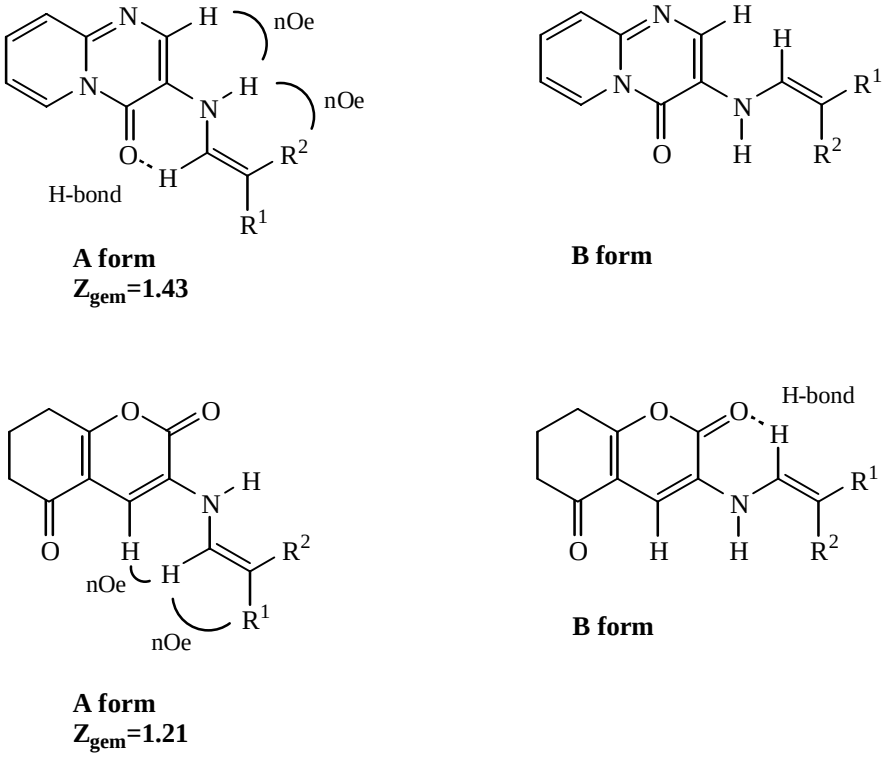
Figure 1



Since 1974, hydrogen bonds of polar CH groups with oxygen, nitrogen or halogen atom have been described extensively.[9-12] The interaction between olefinic proton and ring oxo group in compounds **3-7** is in agreement with those descriptions.

The Z_{cis} value for CN group, with extended conjugation, which is not found in the tables,[13] was determined from experimental shift of olefinic proton and assumption that Z_{gem} for *Z* form of compound **3** is 1.43.

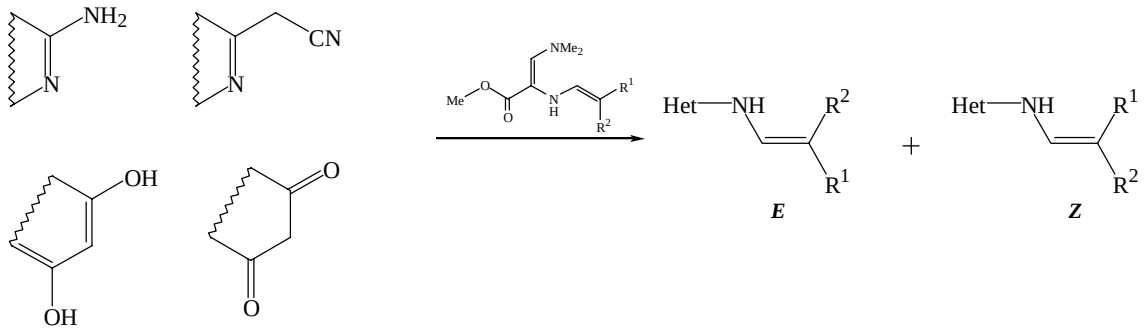
Figure 2. Possible conformers of the heterocycles



The second issue, the conformation of compounds **3-7** can not be determined directly with ^{1}H NMR experiments, therefore NOESY experiments were conducted on selected compounds (entries 12, 15, 24, 27 and 28, *Table 2*). Compounds **3** showed NOE effect between H-C(2) proton and enamino group, while compounds **6** showed NOE effect between H-C(4) proton and olefinic proton, indicating that both types of compounds exist in less hindered A form (*Figure 2*). The origin of the difference is the hydrogen bond between the ring oxo group and olefinic proton, which is present in pyridopyrimidine series.

Entries 21 and 22, namely 2*H*-1-benzopyranones, with methyl group attached at position 4 has Z_{gem} value 1.43, indicating that these compounds exist in B form (*Figure 2*), due to steric hindrance and feature a hydrogen bond between the ring oxo group and olefinic proton.

Table 2. Chemical shifts for NH and CH groups and Z/E ratio



Entry	Het	R_1	R_2	δNH		δC*H*NH		Z/E
				Z	E	Z	E	
1[4]	2-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	COOEt	**		8.40		/
2[4]	2,8-Dimethyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	COOEt	**		8.38		/
3[4]	7-Chloro-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	COOEt	**		8.42		/
4[4]	7,9-Dibromo-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	COOEt	**		8.40		/
5[4]	9-Hydroxy-2-methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	COOEt	**		8.38		/

Entry	Het	R_1	R_2	δNH		δC*H*NH		Z/E
				Z	E	Z	E	
6[3]	4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COMe	COMe	12.61		8.66		/
7[3]	8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COMe	COMe	12.58		8.64		/
8[3]	7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COMe	COMe	12.58		8.65		/
9[5]	4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOMe	COMe	*	12.68	*	8.77	10/90
10[5]	8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOMe	COMe	10.85	12.66	8.66	8.75	10/90
11[5]	7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOMe	COMe	10.88	12.66	8.68	8.76	10/90
12[5]	4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOBn	COMe	/	12.68	/	8.85	0/100
13[5]	8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOBn	COMe	/	12.69	/	8.83	0/100
14[5]	7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOBn	COMe	/	12.70	/	8.80	0/100
15[7]	4-Oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	CN	10.87	10.40	8.71	8.54	67/33
16[7]	8-Methyl-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	CN	10.86	10.32	8.67	8.49	67/33
17[7]	7-Chloro-4-oxo-4*H*-pyrido[1,2-*a*]pyrimidin-3-yl	COOEt	CN	10.86	10.46	8.72	8.56	67/33
18[3]	1-Cyano-4-oxo-4*H*-pyrido[1,2-*a*]pyridin-3-yl	COMe	COMe	12.77		8.58		/
19[5]	1-Cyano-4-oxo-4*H*-pyrido[1,2-*a*]pyridin-3-yl	COOBn	COMe	*	12.85	*	8.76	9/91
20[7]	1-Cyano-4-oxo-4*H*-pyrido[1,2-*a*]pyridin-3-yl	COOEt	CN	9.06	11.00	8.68	8.32	85/15
21[4]	4-Methyl-5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COOEt	COOEt	10.30		8.38		/
22[4]	4,7,7-Trimethyl-5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COOEt	COOEt	10.32		8.42		/
23[3]	5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COMe	COMe	12.37		8.48		/
24[3]	7,7-Dimethyl-5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COMe	COMe	12.37		8.48		/
25[5]	7,7-Dimethyl-5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COOMe	COMe	*	12.34	*	8.50	11/89
26[5]	5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COOBn	COMe	*	12.36	*	8.55	13/87
27[5]	7,7-Dimethyl-5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COOBn	COMe	10.69	12.36	8.46	8.57	12/88

Entry	Het	R_1	R_2	δNH		δC*H*NH		Z/E
				Z	E	Z	E	
28[7]	5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COOEt	CN	10.68	10.34	8.75	8.70	76/24
29[7]	7,7-Dimethyl-5,6,7,8-tetrahydro-2,5-dioxo-2*H*-1-benzopyran-3-yl	COOEt	CN	10.68	10.34	8.76	8.70	78/22
30[3]	5,7-Dihydroxy-2-oxo-2*H*-1-benzopyran-3-yl	COMe	COMe	12.49		8.46		/
31[5]	5,7-Dihydroxy-2-oxo-2*H*-1-benzopyran-3-yl	COOMe	COMe	*	12.47	8.44	8.48	10/90
32[5]	5,7-Dihydroxy-2-oxo-2*H*-1-benzopyran-3-yl	COOBn	COMe	10.36	12.47	8.45	8.54	12/88
33[5]	7-Hydroxy-8-methyl-2-oxo-2*H*-1-benzopyran-3-yl	COOBn	COMe	/	12.55	/	8.57	0/100
34[7]	5,7-Dihydroxy-2-oxo-2*H*-1-benzopyran-3-yl	COOEt	CN	10.73	/	8.67	/	100/0

* Unambiguous determination was impossible, due to the overlaping of the signals.
** ^{1}H NMR spectra of entries 1-5 were recorded in deuterated trifluoracetic acid, therefore the signals for NH are not visible; entries 6-34 were recorded in deuterated dimethylsulphoxyde;
Reference for the synthesis of compound is given at each entry.

Table 3. Z values for the selected groups

	COOR	COOBn	COR	CN	2-oxo-Het-3-NH-	4-oxo-Het-3-NH-
Z_{cis}	1.18	1.25	1.12	1.47	/	/
Z_{trans}	0.55	/	0.87	/	/	/
Z_{gem}	/	/	/	/	1.21	1.43

Conclusions

Z_{gem} values, calculated from the NMR data of numerous compounds can be useful criteria for determination of conformers in described series of heterocyclic compounds. In addition, orientation on enamino double bond on the analoguous systems can be easily determined by the means of basic ^{1}H NMR experiment and with the aid of the tables presented in this article.

Acknowledgements

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References and Notes

1. G. Soršak, A. Sinur, L. Golič, B. Stanovnik, *J. Heterocycl. Chem.*, **1995**, *32*, 921.
2. R. Toplak, L. Selič, G. Soršak, B. Stanovnik, *Heterocycles* **1997**, *45*, 555.
3. L. Selič, B. Stanovnik, *J. Heterocycl. Chem.*, **1997**, *34*, 813.
4. L. Selič, S. Golič Grdadolnik, B. Stanovnik, *Heterocycles* **1997**, *45*, 2349.
5. L. Selič, S. Golič Grdadolnik, B. Stanovnik, *Helv. Chim. Acta* **1997**, *80*, 2418.
6. S. Strah, B. Stanovnik, S. Golič Grdadolnik, *J. Heterocycl. Chem.*, **1997**, *34*, 263.
7. L. Selič, S. Golič Grdadolnik, B. Stanovnik, *Heterocycles* **1998**, *49*, 133.
8. S. Nigishaki, M. Ichiba, K. Shikomura, F. Yoneda, *J. Heterocycl. Chem.*, **1971**, *8*, 759.
9. R. D. Green, *Hydrogen Bonding by C-H Groups*, Wiley Interscience, New York, 1974.
10. D. J. Sutor, *J. Chem. Soc.*, **1963**, 1105.
11. R. Taylor, O. Kennard, *J. Am. Chem. Soc.*, **1982**, *104*, 5063.
12. Harlow, R.; Li, C.; Sammes, M. P. *J. Chem. Soc.; PT I*, **1984**, 547.
13. M. Hesse, H. Meier, B. Zeeh, *Spectroscopic Methods in Organic Chemistry*, Georg Thieme Verlag, Stuttgart – New York, 1997, pp. 122.

Povzetek

Dve strukturni značilnosti, in sicer orientacija na enaminski dvojni vezi in relativna postavitev skupin na 3-amino skupini, na seriji 3-(2,2-disubstituiranih etenil)amino-substituiranih heterociklov, kot so npr. 4*H*-pirido-[1,2-*a*]pirimidin-4-oni **3**, 5*H*-tiazolo[3,2-*a*]pirimidin-5-oni **4**, 4*H*-pirido[1,2-*a*]piridin-4-oni **5**, 5,6,7,8-tetrahydro-2*H*-1-benzopiran-2-oni **6** and 2*H*-1-benzopiran-2-oni **7**, sta bili razrešeni s pomočjo osnovnih ^{1}H NMR eksperimentov.