Substituent effect on proton chemical shifts of amide and azomethine groups of arylidenehydrazides of 5-substituted 2-pyrimidine-carboxylic acids and their aromatic analogs

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Influence of the substituent electronic effects on the chemical shifts of protons of the amide and azomethine groups of four series of compounds – benzylidenehydrazides of 5-substituted 2-pyrimidinecarboxylic and *para*-substituted benzoic acids, *para*-substituted benzylidenehydrazides of 2-pyrimidinecarboxylic and benzoic acids – has been investigated. It has been shown that there is a linear relationship between the chemical shifts of protons of the amide and azomethine groups and F, R constants of substituents. The sensitivity of the chemical shift of the amide group to the substituent effects of the hydrazide part was found to be similar to that of the aldehyde part of the compounds studied.

Key words: arylidenehydrazides of 2-pyrimidinecarboxylic acids, ^{1}H NMR spectra, substituent effect, correlation analysis

INTRODUCTION

Acylhydrazones possess a broad spectrum of physiological activity [1–9]. Some of the synthesized by us arylidenehydrazides of pyrimidinecarboxylic acids [10–13] were shown to inhibit monoaminoxidase. From the analysis of changes in biological activity and physico-chemical parameters observed in a series of related compounds, it is possible to predict which of the properties are important in expressing biological activity. However, to the best of our knowledge, quantitative data on the relationships between the physico-chemical parameters of arylidenehydrazides of not only pyrimidinecarboxylic acids, but also those of benzoic acids are not available for the present. In this connection we have studied the substituent effect on the proton chemical shift of the amide (CONH) and azomethine (N=CH) groups of arylidenehydrazides of 2-pyrimidinecarboxylic acids and, for comparison, arylidenehydrazides of *para*-substituted benzoic acids.

RESULTS AND DISCUSSION

Four series of compounds have been investigated: benzylidenehydrazides of 5-substituted 2-pyrimidinecarboxylic acids (I) and *para*-substituted benzoic acids (II), bearing substituents in the hydrazide part of the molecule, and *para*-substituted benzylidenehydrazides of 2-pyrimidinecarboxylic (III) and benzoic acid (IV) with substituents in the aldehyde part of the molecule.
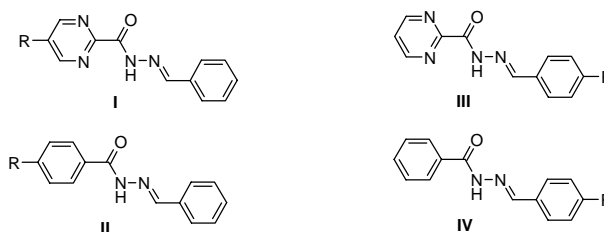
The ^{1}H NMR spectra of compounds I–IV have been measured in dimethyl sulfoxide solutions (DMSO). As a solvent, DMSO has been chosen for several reasons. First of all, insufficient solubility of arylidenehydrazides in such nonpolar solvents as hexane, tetrachloromethane or slightly polar trichloromethane made it impossible to obtain reliable data in the NMR study. Secondly, DMSO is a solvent possessing electronodonating properties and, therefore, minimizes the possibility of formation of hydrogen-bonded associates between the active groups and substituents [14] of the compounds studied. Subsequently, there is no necessity to perform the concentration investigations in order to get chemical shifts at infinite dilution, because the proton chemical shifts of active groups in strongly diluted solu-

Table 1. **Chemical shifts of the NH and N=CH groups of compounds I–IV in DMSO***

R	Series I		Series II		Series III		Series IV	
	δ_{NH}, ppm	$\delta_{N=CH}$, ppm	δ_{NH}, ppm	$\delta_{N=CH}$, ppm	δ_{NH}, ppm	$\delta_{N=CH}$, ppm	δ_{NH}, ppm	$\delta_{N=CH}$, ppm
Me$_2$N	–	–	–	–	11.93	8.48	11.57	8.35
MeO	12.13	8.67	11.76	8.48	12.12	8.58	11.76	8.46
Me	12.22	8.66	11.81	8.49	12.19	8.61	11.82	8.46
H	12.27	8.66	11.89	8.51	12.27	8.66	11.89	8.51
Cl	12.32	8.66	11.95	8.49	12.33	8.65	11.96	8.49
Br	12.31	8.66	11.95	8.49	–	–	–	–
NO$_2$	–	–	–	–	12.56	8.76	12.19	8.59

* Chemical shifts were measured relatively to the methyl groups of DMSO and transferred to TMS scale using expression $\delta = \delta_{DMSO} + 2.59$.

Table 2. **Parameters of the correlation equations $\delta = \delta_o + fF + rR$**

Eq. No.	Series	δ	δ_o	f	r	R*	n
1	I	δ_{NH}	12.28 ± 0.006	0.24 ± 0.019	0.41 ± 0.022	0.990	5
2	II	δ_{NH}	11.88 ± 0.006	0.31 ± 0.02	0.41 ± 0.02	0.992	5
3	III	δ_{NH}	12.26 ± 0.011	0.33 ± 0.028	0.41 ± 0.019	0.994	6
4	IV	δ_{NH}	11.89 ± 0.01	0.34 ± 0.02	0.39 ± 0.02	0.996	6
5	III	$\delta_{N=CH}$	8.65 ± 0.009	0.11 ± 0.021	0.20 ± 0.015	0.983	6
6	IV	$\delta_{N=CH}$	8.497 ± 0.015	0.093 ± 0.036	0.16 ± 0.025	0.930	6

*Correlation coefficient.

tions are concentration-independent and reflect the monomeric state of molecules [15]. This has been also observed in the investigation of 5-substituted 2-pyrimidinecarboxylic acid hydrazides [16].

In the ^{1}H NMR spectra of compounds I–IV, along with the signals of the aromatic protons of the pyrimidine and benzene ring signals of protons of the NH and N=CH groups are being observed with the values of chemical shifts presented in Table 1.

In order to evaluate quantitatively the effect of substituents on the proton chemical shifts of the NH and N=CH groups in compounds I–IV, we have performed the two-parameter correlation (Table 2) of the *d* values of the aforementioned groups with the modified according to [17] substituent constants F, R of Swain and Lupton [18] according to the following equation:

$$\delta = \delta_o + fF + rR,$$

where *f* and *r* are the parameters evaluating the sensitivity of proton chemical shift to the change of the substituent nature, characterised by F, R constants of Swain and Lupton and δ_o is a free member.

These constants were shown to be effective in deducing the mechanism of transmission of the substituent electronic effects on a reaction centre [19–21].

Data presented in Tables 1 and 2 indicate the chemical shift $\delta_{N=CH}$ of compounds I and II to be not sensitive and that of compound III, IV little sensitive (eq. 5, 6) to the electronic effects of the substituents as in the hydrazide and aldehyde part

of the molecules. This is caused by the large distance between the substituent and the resonating proton, by the isolating effect of the amide group [22] (series I and II), as well as by a little polarity of the C–H bond of the azomethine group. A similar result was obtained in the investigation of the substituent effect on the proton chemical shift of N=CH group of benzylideneanilines [15, 23]. The higher sensitivity of the NH chemical shift of compounds I–IV (eq. 1–4) to the substituent effects in comparison with $\delta_{N=CH}$ (eq. 5, 6) can be explained by the enhanced polarity of the N–H bond, caused by the processes of formation of hydrogen-bonded complexes between the hydrogen of the indicated group and molecules of solvent.

From the analysis of equations 1–4 (Table 2) it follows that transmission of the resonance effect of substituents through the amide (series I and II) and the hydrazone (series III and IV) groups is not high and almost identical. Insignificant differences are connected with the inductive component. If the inductive influence of substituents on the electronic shielding of the NH group proton has been transmitted only through the bonds, the proton chemical shift of the mentioned group should have to be more sensitive to the inductive effect in the series I and II than in the series III and IV. However, in spite of the greater distance between the resonating proton and the substituent R in the series III and IV, the influence of the inductive effect on the proton chemical shift of the NH group remains almost the same as in the series II, and increases insignificantly in comparison to the series I. Taking into account that the

Table 3. **Data of benzylidenehydrazides of 5-substituted 2-pyrimidinecarboxylic acids (I)**

R (yield, %)	M. p., °C (solvent)	Formula	Found / Calculated, %		
			C	H	N
MeO	199–200	$C_{13}H_{12}N_4O_2$	61.05	4.72	21.94
(87)	(methanol)		60.93	4.72	21.86
Me	198–199	$C_{13}H_{12}N_4O$	64.71	4.95	23.39
(86)	(ethanol)		64.99	5.03	23.32
Cl	218.5–219	$C_{12}H_9ClN_4O$	55.61	3.82	21.85
(92)	(2-propanol)		55.29	3.48	21.49
Br	220.5–222	$C_{12}H_9BrN_4O$	46.92	3.12	18.38
(90)	(2-propanol)		46.71	3.00	18.54

Table 4. **Data of arylidenehydrazides of 2-pyrimidinecarboxylic acids (III)**

R (yield, %)	M. p., °C (solvent)	Formula	Found / Calculated, %		
			C	H	N
Me_2N	184–185	$C_{14}H_{15}N_5O$	62.71	5.98	26.40
(67)	(ethanol)		62.44	5.61	26.01
MeO	162–163	$C_{13}H_{12}N_4O_2$	61.16	4.62	22.18
(62)	(ethanol)		60.93	4.72	21.86
Me	218–219	$C_{13}H_{12}N_4O$	65.22	4.66	23.27
(76)	(ethanol)		64.99	5.03	23.32
H	180–181	$C_{12}H_{10}N_4O$	63.97	4.49	25.07
(78)	(ethanol)		63.71	4.45	24.76
Cl	242–243	$C_{12}H_9ClN_4O$	55.05	3.23	21.72
(64)	(propanol)		55.29	3.48	21.49
NO_2	269–270	$C_{12}H_9N_5O_3$	53.55	2.98	25.56
(61)	(dimethylformamide)		53.14	3.34	25.82

substituent constant F includes the inductive effect acting through σ bonds and space (field effect) [19], it is possible to suppose that in this case a considerable role belongs the field component, which at certain configuration of arylidenehydrazides in the series III and IV may be predominant over the field component in the series I and II.

EXPERIMENTAL

Melting points were determined in open capillaries and are uncorrected. ^{1}H-NMR spectra were recorded with a TESLA BS 587A spectrometer (80 MHz) at a temperature of 33 °C. For every compound 3–5 measurements were carried out. The concentration of compounds I–IV were 0.005 m. f. DMSO was purified as described in [24] and dried by storing over molecular sieves 4A. The samples for NMR measurements were prepared in a box preliminary dried with magnesium perchlorate. All reactions and purity of the synthesized compounds were monitored by TLC using Silica gel 60 F_{254} aluminium plates (Merck). Visualization was accomplished in UV light.

Benzylidenehydrazides of 5-substituted 2-pyrimidinecarboxylic acids (I) and arylidenehydrazides of 2-pyrimidinecarboxylic acid (III). To a hot solution of the corresponding hydrazide (10 mmol) [16] in ethanol, aromatic aldehyde (15 mmol) was added and the reaction mixture was refluxed for 3–5 h. After cooling to room temperature the precipitate was filtered off, washed with ethanol and recrystallised to give compounds I, III. Data of the synthesised compounds are presented in Tables 3, 4.

Benzylidenehydrazides of 4-substituted benzoic acids (II) and arylidenehydrazides of benzoic acid (IV) were synthesised according to the above procedure. Their characteristics were in agreement with those reported in reference [25].

CONCLUSIONS

A linear relationship has been shown to exist between the proton chemical shifts of the amide and azomethine groups of benzylidenehydrazides of 5-substituted 2-pyrimidinecarboxylic and *para*-substituted benzoic acids, *para*-substituted benzylidenehydrazides of 2-pyrimidinecarboxylic and benzoic acids and the F, R substituent constants. The amide and hydrazone bridges in the arylidenehydrazides reduce the substituent effects to a comparable extent.

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PAKAITØ ÁTAKA 5-PAKEISTØ 2-PIRIMIDINKARBOK-SIRÛGÐÈIØ ARILIDENHIDRAZIDØ IR JØ AROMATINIØ ANALOGØ AMIDINËS IR AZOMETININËS GRUPIØ PROTONØ CHEMINIAMS POSLINKIAMS

S a n t r a u k a

Iðtirta pakaitø elektroniniø efektø átaka keturiø serijø junginiø – 5-pakeistø 2-pirimidinkarboksi- ir *para*-pakeistø benzenkarboksirûgðèiø benzilidenhidrazidø, 2-pirimidinkarboksi- ir benzenkarboksirûgðèiø *para*-pakeistø benzilidenhidrazidø amidinës ir azometininës grupiø protonø cheminiams poslinkiams. Nustatyta, kad amidinës ir azometininës grupiø protonø cheminiai poslinkiai tiesiðkai koreliuoja su pakaitø F, R konstantomis. Arilidenhidrazidø amidinis ir hidrazoninis fragmentai panaðiai slopina pakaitø elektroninius efektus.