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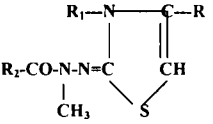
Department of General Chemistry, Medical University of Lublin

LIDIA BIELAK, MAŁGORZATA KIEŁCZYKOWSKA,
KAZIMIERZ PASTERNAK

The acid-base equilibrium of 3-R_1-4-R-thiazol-2-one hydrazone derivatives. V. *Ionization constants of α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazides of picolinic, nicotinic and isonicotinic acids*

As the continuation of our previous studies concerning the acid-base equilibrium of thiazol-2-one derivatives (1, 2, 3, 4) the α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazides of picolinic, nicotinic and isonicotinic acids were obtained by the reaction of 1,4-dimethylthiosemicarbazides with chloroacetone and their dissociation constants were determined spectrophotometrically. The attempts at the synthesis of the studied compounds by the reaction of methylhydrazone of 3,4-dimethylthiazol-2-one with the chlorides of pyridinecarboxylic acids using benzene, pyridine or acetic acid medium remained unsuccessful. However, the hydrolysis of the compounds I-P, I-N and I-IN in 15% HCl resulted in methylhydrazone of 3,4-dimethylthiazol-2-one hydrochloride. The mixture of the compound obtained in this way with the one synthesized by the reaction of 1,4-dimethylthiosemicarbazide with chloroacetone (2) does not show the depression of the melting point. This fact, in our opinion confirms the structure of the studied derivatives.



I-P, $R_1 = R = CH_3$, $R_2 = 2\text{-}C_5H_4N$
I-N, $R_1 = R = CH_3$, $R_2 = 3\text{-}C_5H_4N$
I-IN, $R_1 = R = CH_3$, $R_2 = 4\text{-}C_5H_4N$

MATERIAL AND METHODS

SYNTHESIS OF THE COMPOUNDS

1.1,4-dimethyltiosemicarbazides of nicotinic and isonic--otinic acid. 1.51 g (0.01 mol) of α-methylhydrazide of the proper acid and 0.73 (0.01 mol) of methyl isothiocyanate were heated in 50 cm^3 of diethyl ether (in the case of nicotinic derivative for 5 h, isonicotinic one – 2 h). The obtained precipitate was filtered off and crystallized. The solvents, crystalline forms, melting points, yields and the results of the analysis were as follows:

1,4-dimethylthiosemicarbazide of nicotinic acid (1-N):

2-propanol, prisms, 158–160°C, 1.25 g (56%).

Analysis for the formula $C_9H_{12}N_4OS$:

Calculated: 48.15%C; 5.35%H, 24.98%N

Obtained: 48.05%C, 5.27%H, 24.96%N.

1,4-dimethylthiosemicarbazide of isonicotinic acid (1-IN):

2-propanol, prisms, 161–162°C (dec.), 1.48 g (66%).

Analysis for the formula $C_9H_{12}N_4OS$:

Calculated: 48.15%C; 5.35%H, 24.98%N

Obtained: 48.44%C, 5.36%H, 24.69%N.

The results of IR and H-NMR spectrometry for the compounds 1-N and 1-IN are presented in Table 1. 1,4-dimethylthiosemicarbazides of the studied acids, similarly as previously obtained 1,4-dimethylthiosemicarbazide of picolinic acid, heated in water for 4 h are subject to cyclization to the respective mesoionic 1,4-dimethyl-5-pyridyl-3-thio-1,3,4-triazoles (5).

Table 1. IR and H-NMR spectra of 1,4-dimethylthiosemicarbazides of nicotinic and isonicotinic acid

Compound	IR (cm^{-1})		H-NMR Spectrum	
	C=O Amide I	N-H	Solvent	(ppm)
1-N	1675	3282	$(CD_3)_2CO$	3.07 (s, 3H, CH_3-NH); 3.23 (s, 3H, CH_3-N); 7.36-7.41 (m, 1H, β); 7.87-7.90 (d, 1H, γ); 8.59-8.62 (m, 1H, α); 8.70-8.71 (d, 1H, α); 9.00 (s, 1H, NH)
1-IN	1676	3281	DMSO-d6	2.90 (s, 3H, CH_3-NH); 3.10 (s, 3H, CH_3-N); 7.34 (s, 2H, β); 8.62-8,63 (d, 2H, α); 9.70 (s, 1H, NH)

The structure of the obtained 1,3,4-triazoles was identified examining the percentage of C, H and N:

Calculated: 52.40%C; 4.88%H; 27.16%N

Obtained:

1,4-dimethyl-5-(3-pyridyl)-3-thio-1,3,4-triazole 52.46%C, 4.83%H, 27.01%N,

1,4-dimethyl-5-(4-pyridyl)-3-thio-1,3,4-triazole 52.60%C, 4.60%H, 27.30%N.

The mixtures with the respective compounds obtained in the way described previously (5) do not show the depression of the melting points.

2. α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazides of picolinic, nicotinic and isonicotinic acids

2.1. α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazide of picolinic acid (I-P)

The mixture of 1.12 g (0.005 mol) of 1,4-dimethylthiosemicarbazide of picolinic acid (4) and 1.2 cm^3 (0.015 mol) of chloroacetone was heated in 15 cm^3 of methanol for 3 h. The excess of diethyl ether was added and the formed precipitate was separated, dissolved in water and neutralized with saturated Na_2CO_3 solution. The solvent was evaporated and acetone was added to the residue. After filtration the acetone was evaporated and 10 cm^3 of the mixture of 2-propanol – hexane (2:3) was added to the obtained oil. The formed precipitate was crystallized from the same mixture.

Colourless cubes, m.p. 128–130°C, yield 0.53 g (40%).

Analysis for the formula $C_{12}H_{14}N_4OS$:

Calculated: 54.95%C; 5.38%H, 21.36%N

Obtained: 54.84%C, 5.36%H, 21.39%N.

2.2. Dihydrochloride of α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazide of nicotinic acid (I-N · 2HCl)

The mixture of 1.7 g (0.0076 mol) of 1,4-dimethylthiosemicarbazide of nicotinic acid (1-N) and 1.2 cm^3 (0.015 mol) of chloroacetone was heated in 25 cm^3 of methanol for 5 h. The solvent was evaporated and 2-propanol was added to the obtained oil. After the solidification the precipitate was crystallized from the mixture of 2-propanol – ethanol (4 : 1).

Colourless cubes, m.p. 212–214°C, yield 1.50 g (60%).

Analysis for the formula $C_{12}H_{14}N_4OS \cdot 2HCl$:

Calculated: 43.32%C; 4.81%H, 16.71%N

Obtained: 43.70%C, 4.84%H, 16.78%N.

2.3. α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazide of isonicotinic acid (I-IN)

The mixture of 1.12 g (0.005 mol) of 1,4-dimethylthiosemicarbazide of isonicotinic acid (1-IN) and 1.2 cm^3 (0.015 mol) of chloroacetone was heated in 15 cm^3 of methanol for 3 h. The solvent was evaporated and 2-propanol was added to the residue. Yellow precipitate of hydrochloride was filtered and crystallized from 2-propanol.

Yellow plates, m.p. 209–211°C, yield 0.65 g (50%).

Analysis for the formula $C_{12}H_{14}N_4OS \cdot HCl$:

Calculated: 48.19%C; 4.35%H, 18.74%N

Obtained: 48.08%C, 4.04%H, 18.42%N.

1.0 g of hydrochloride was dissolved in 10 cm^3 of water and neutralized with solid Na_2CO_3. The obtained precipitate was crystallized from the mixture of benzene – hexane (2 : 1). Colourless plates, m.p. 158–160°C, yield 0.65 g (77%).

Analysis for the formula $C_{12}H_{14}N_4OS$:

Calculated: 54.95%C; 5.38%H, 21.36%N

Obtained: 55.04%C, 5.32%H, 21.06%N.

The results of IR and H-NMR spectrometry for the compounds I-P, I-N, I-IN are presented in Table 2.

Table 2. IR and H-NMR spectra of compounds I-P, I-N, I-IN

Compound	IR C=O Amide I (cm^{-1})	H-NMR [ppm]	
		Solvent	[ppm]
I-P	1632	$CDCl_3$	2.10 (s, 3H, CH_3-C); 3.10 (s, 3H, CH_3-N-C); 3.35 (s, 3H, CH_3-N-N=); 5.62-5.62 (m, 1H, C=CH); 7.23-7.71 (m, 3H, β, γ); 8.56 (s, 1H, α)
I-N*	1672	DMSO-d6	2.16 (s, 3H, CH_3-C); 3.30 (s, 3H, CH_3-N-C); 3.38 (s, 3H, CH_3-N-N=); 6.50 (s, 1H, C=CH); 7.75-7.80 (m, 1H, β); 8.39-8.41 (d, 1H, γ); 8.80-8.82 (m, 1H, α); 8.97-8.98 (d, 1H, α);
I-IN	1636	$CDCl_3$	2.08 (s, 3H, CH_3-C); 3.15 (s, 3H, CH_3-N-C); 3.32 (s, 3H, CH_3-N-N=); 5.62-5.64 (d, 1H, C=CH); 7.28-7.46 (m, 2H, β); 8.55-8.57 (d, 2H, α)

* Data obtained for the dihydrochloride form

SPECTOPHOTOMETRICAL MEASUREMENTS

The basic solutions of the studied compounds were prepared by the dissolution of the proper weighted sample in methanol. The work solutions in 20% (v/v) methanol were prepared by the dilution of the basic solutions with the proper amount of water.

The concentrations of the basic solutions were: $1.5 \cdot 10^{-3}$ mol/dm^3 for I-P compound; $8.0 \cdot 10^{-3}$ mol/ dm^3 for I-N in the case of pK_2 measurement; $4.0 \cdot 10^{-3}$ mol/dm^3 for I-IN and I-N in the case of pK_1 measurement.

The concentrations of the work solutions were: $3.0 \cdot 10^{-4}$ mol/dm^3 for I-P compound; $1.6 \cdot 10^{-3}$ mol /dm^3 for I-N in the case of pK_2 measurement; $8.0 \cdot 10^{-4}$ mol/dm^3 for I-IN and I-N in the case of pK_1 measurement.

For each compound the measurement series of solutions with the stable concentration and different pH was prepared. The content of methanol was established as 2% (v/v). The concentrations were established as follows: $3.0 \cdot 10^{-5}$ mol/dm^3 for I-P in the case of both pK_1 and pK_2 measurement; $8.0 \cdot 10^{-5}$ mol/dm^3 for I-N in the case of pK_1 measurement and $1.6 \cdot 10^{-4}$ mol/dm^3 for I-N in the case of pK_2 measurement. $8.0 \cdot 10^{-5}$ mol/dm^3 for I-IN in the case of both pK_1 and pK_2 measurement;

For each solution of the measurement series the pH value and the absorption spectrum from 230 nm were determined. The cuvette width was 5 cm. The measurements were performed with the help of spectrophotometer SPECORD M40 (Zeiss Jena) and pH-meter RADELKIS OP 208/1. The results (pK values and analytical wave lengths) are presented in Table 3.

Table 3. The dissociation constants of compounds I-P, I-N, I-IN

Compound	Reaction	λ_{anal} [nm]	pK
I-P	$LH_2^{2+} = LH^+ + H^+$		< 1
	$LH^+ = L + H^+$	290	3.44 ± 0.10
I-N	$LH_2^{2+} = LH^+ + H^+$	308	2.20 ± 0.15
	$LH^+ = L + H^+$	354	3.73 ± 0.15
I-IN	$LH_2^{2+} = LH^+ + H^+$	322	1.98 ± 0.10
	$LH^+ = L + H^+$	368	4.06 ±0.10

RESULTS

The pK_1 values are connected with the dissociation of the dication forms. This process takes place at pH about 2 in the case of derivatives of nicotinic and isonicotinic acids, whereas in the case of picolinic one it occurs in the strongly acidic medium (pH < 1). The pK_2 values related to the dissociation of monocation forms range from 3.4 to 4.1. In this case there is no significant difference among the studied compounds (Table 3). The comparison of the spectra of dications, monocations and neutral molecules shows that the curves of dication and monocation forms of I-P differ from the respective ones of the other derivatives (Fig. 1 and Fig. 2). In the case of neutral molecules no significant differences were observed (Fig. 3).

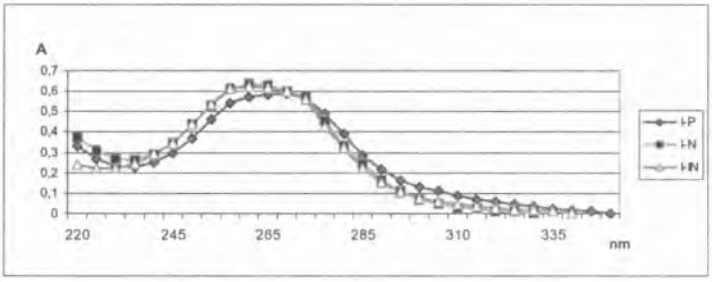


Fig. 1. The absorption spectra of the dications of compounds I-P, I-N, I-IN

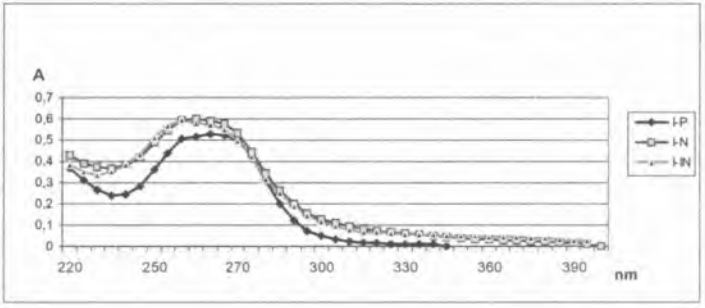


Fig. 2. The absorption spectra of the monocations of compounds I-P, I-N, I-IN

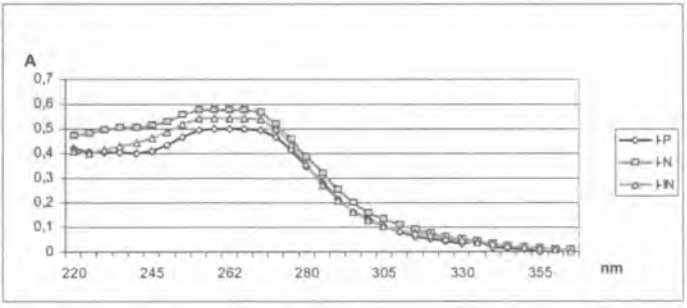


Fig. 3. The absorption spectra of the neutral molecules of compounds I-P, I-N, I-IN

DISCUSSION

The comparison of the obtained pK values shows that there is a significant difference between the pK_1 value of the α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazide of picolinic acid (I-P) and the respective values for the other described derivatives. Such phenomenon has already been noticed in the case of the previously studied compounds (1, 4). What's more, it has concerned not only the derivatives of the analogical structure but also the isomeric 2-phenylimino-3-methylpicolinoyloamino-4-phenyl-4-thiazoline (4). It could point to any kind of interaction occurring in the hydrazides or amides of picolinic acid which results in the higher stability of the monocation form. This effect could be regarded as the reason of the high value of pK_1 – the binding of H^+ by the monocation is probably connected with the destruction of the stabilizing interaction and requires the higher concentration of H^+ (significant lower pH value).

This is why we ascribed the pK_1 value to the process of disconnection of H^+ ion from the nitrogen atom included into pyridine ring and pK_2 value to the disconnection of H^+ from N^3 atom in thiazoline ring. We suggest that the nitrogen atoms in the chain between the heterocyclic rings cannot bind H^+ ions because of the steric hindrance.

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SUMMARY

The α-methyl-β-(3,4-dimethylthiazol-2-ylidene)-hydrazides of picolinic (I-P), nicotinic (I-N) and isonicotinic (I-IN) acids were obtained and their ionization constants were determined spectrophotometrically in aqueous solutions:

I-P	$pK_1 < 1$	$pK_2 = 3.44 \pm 0.10$
I-N	$pK_1 = 2.20 \pm 0.15$	$pK_2 = 3.73 \pm 0.15$
I-IN	$pK_1 = 1.98 \pm 0.10$	$pK_2 = 4.06 \pm 0.10$.

The spectra of dications, monocations and neutral molecules of the studied compounds were also presented.

Równowaga kwasowo-zasadowa pochodnych hydrazonu 3-R_1-4-R-tiazol-2-onu. V. Stałe jonizacji α-metylo-β-(3,4-dimetylotiazol-2-ilideno)-hydrazydów kwasu pikolinowego, nikotynowego i izonikotynowego

Przeprowadzono syntezę α-metylo-β-(3,4-dimetylotiazol-2-ilideno)-hydrazydów kwasów pikolinowego (I-P), nikotynowego (I-N), izonikotynowego (I-IN), a następnie wyznaczono ich stałe dysocjacji metodą spektrofotometryczną w środowisku wodnym:

I-P	$pK_1 < 1$	$pK_2 = 3.44 \pm 0.10$
I-N	$pK_1 = 2.20 \pm 0.15$	$pK_2 = 3.73 \pm 0.15$
I-IN	$pK_1 = 1.98 \pm 0.10$	$pK_2 = 4.06 \pm 0.10$.

Przedstawiono również widma dikationów, monokationów i cząstek obojętnych omawianych związków.