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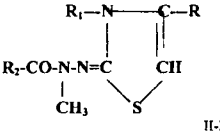
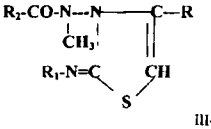
Ionization constants of 2-phenylimino-3-methylpyridoyloamino-4-phenyl-4-thiazolines and α-methyl-β-(3-phenyl-4-methylthiazol-2-ylidene)-hydrazides of nicotinic and isonicotinic acids

Aiming at finishing the series of the studies concerning the tautomerism and acid-base equilibrium of thiazole and thiazoline derivatives of different carboxylic acids we obtained 2-phenylimino-3-methylpyridoyloamino-4-phenyl-4-thiazolines and α-methyl-β-(3-phenyl-4-methylthiazol-2-ylidene)-hydrazides of nicotinic and isonicotinic acids.



II-N, $R_1 = C_6H_5$, R = CH_3, $R_2 = 3\text{-}C_5H_4N$
II-IN, $R_1 = C_6H_5$, R = CH_3, $R_2 = 4\text{-}C_5H_4N$



III-P $R_1 = C_6H_5$, R = CH_3, $R_2 = 2\text{-}C_5H_4N$
III-N $R_1 = C_6H_5$, R = CH_3, $R_2 = 3\text{-}C_5H_4N$

III-IN $R_1 = C_6H_5$, R = CH_3, $R_2 = 4\text{-}C_5H_4N$

MATERIAL AND METHODS

SYNTHESIS OF THE COMPOUNDS

1. 2-phenylimine-3-methylamine-4-methyl-4-thiazoline hydrochloride

2.61 g (0.01 mol) of 2-phenylimino-3-acetylmethylamine-4-phenyl-4-thiazoline (2) in 40 cm^3 of HCl (6 mol/dm^3) was heated for 2 h. The solvent was evaporated. 10 cm^3 of 2-propanol and the excess of diethyl ether were added to the residue (oil). The obtained precipitate was filtered off and crystallized from 2-propanol.

Colourless plates, m.p. 203-205°C, yield 1.35 g (50%).
Analysis for the formula $C_{11}H_{13}N_3S \cdot HCl$:
Calculated: 51.65%C; 5.51%H, 16.53%N
Obtained: 51.68%C, 5.30%H, 16.23%N.

2. 2-phenylimino-3-methylpicolinoylamino-4-methyl-4-thiazoline (III-P)

2a. 1.1 g (0.005 mol) of unpurified 2-phenylimine-3-methylamine-4-methyl-4-thiazoline (oil obtained by neutralization of water solution of the compound obtained in point 1 with concentrated $NH_{3(aq)}$) in 20 cm^3 of dry benzene and 0.8 g (0.005 mol) hydrochloride of picolinic acid chloride were heated in 70-80°C for 3 h. The obtained precipitate was filtered off, dissolved in methanol and the obtained solution was heated with addition of active carbon. Methanol was evaporated, the residue was neutralized with 25% aqueous ammonia solution. The obtained precipitate was crystallized from 2-propanol.

Colourless plates, m.p. 132-134°C, yield 0.25 g (15%).
Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 62.68%C, 5.04%H, 17.40%N.

2b. The mixture of 1.34 g (0.005 mol) of 1-methyl-4-phenylthiosemicarbazide of picolinic acid and 0.70 cm^3 (0.01 mol) of chloroacetone in 20 cm^3 of methanol was heated for 3 h. The solution was concentrated to 1/3 of volume and neutralized with saturated aqueous CH_3COONa solution. The obtained precipitate was filtered off and crystallized from the mixture ethanol–water (2:1).

Colourless plates, m.p. 132-134°C, yield 0.60 g (35%).
Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 62.76%C, 5.42%H, 16.88%N.

The mixture with the compound obtained in point 2a does not show the depression of melting point.

3. 2-phenylimino-3-methylnicotinoylamino-4-methyl-4-thiazoline (III-N)

3a. 1.1 g (0.005 mol) of unpurified 2-phenylimine-3-methylamine-4-methyl-4-thiazoline (oil) in 20 cm^3 of dry benzene and 0.8 g (0.005 mol) hydrochloride of nicotinic acid chloride were heated in 70-80°C for 3h. The obtained precipitate was filtered off, dissolved in water and neutralized with 25% aqueous ammonia solution. A small amount of 2-propanol was added to the obtained oil and the formed precipitate was crystallized from the mixture 2-propanol-water (1:1).

Colourless plates, m.p. 114-116°C, yield 0.25 g (15%).
Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 62.84%C, 4.97%H, 17.29%N.

4. 2-phenylimino-3-methylisonicotinoylamino-4-methyl-4-thiazoline (III-IN)

4. 1.1 g (0.005 mol) of unpurified 2-phenylimine-3-methylamine-4-methyl-4-thiazoline (oil) in 20 cm^3 of dry benzene and 0.8 g (0.005 mol) hydrochloride of isonicotinic acid chloride were heated in 70-80°C for 3 h. The obtained precipitate was filtered off, dissolved in water and neutralized with 25% aqueous ammonia solution. The obtained oil was extracted with chloroform and after removing the solvent the oil was added with a small amount of 2-propanol. The obtained precipitate crystallized from 2-propanol.

Colourless plates, m.p. 137-139°C, yield 0.25 g (15%).
Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 62.52%C; 5.40%H; 17.30%N.

5. α-methyl-β-(3-phenyl-4-methylthiazol-2-ylidene)-hydrazide of nicotinic acid (II-N), 2-phenylimino-3-methylnicotinoylamino-4-methyl-4-thiazoline (III-N) and *mesoionic* 1-methyl-4-phenyl-3-thio-5-(3-pyridyl)-1,2,4-triazole

The mixture of 2 g (0.007 mol) 1-methyl-4-phenylthiosemicarbazide of nicotinic acid (3) and 1.4 cm^3 (0.016 mol) of chloroacetone in 25 cm^3 of methanol was heated for 5 h. Methanol was evaporated and the residue was added with 15 cm^3 of 2-propanol. The solution was cooled and filtered off.

Precipitate: yellow hydrochloride was dissolved in 15 cm^3 of water and neutralized with solid Na_2CO_3. After crystallization from the mixture of benzene: hexane (2:3) – compound II-N.

Colourless cubes, m.p. 98-100°C, yield 0.55 g (24%).
Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 63.00%C; 5.18%H; 17.42%N.

The 2-propanol filtrate: (after removing the yellow precipitate of hydrochloride) the solution was removed and the residue was dissolved in small amount of water and the obtained solution was neutralized by 50% NaOH. The obtained oil was separated and dissolved in 2-propanol. The solution was cooled and the formed precipitate was filtered and crystallized from ethanol–*mesoionic* 1-methyl-4-phenyl–3-thio-5-(3-pyridyl)-1,2,4-triazole.
Colourless prisms, m.p. 296–297°C, yield 0.20 g (10%).

The mixture with the previous obtained compound (4) does not show the depression of melting point. IR and UV spectra of both compounds do not show any differences.
The 2-propanol filtrate (obtained after separating the mesoionic triazolothione) was diluted with the excess of water and the formed precipitate was filtered off and crystallized from the mixture of 2-propanol–water (1:1) – colourless plates, m.p. 114–116°C, yield 0.24 g (10%) –compound III-N.

Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 62.45%C; 4.90%H; 16.90%N.

The mixture with the compound obtained in point 3 does not show the depression of the melting point.

6. α-methyl-β-(3-phenyl-4-methylthiazol-2-ylidene)-hydrazide of isonicotinic acid (II-IN), 2-phenylimino-3-methylisonicotinoylamino-4-methyl-4-thiazoline (III-IN) and *mesoionic* 1-methyl-4-phenyl-3-thio-5-(4-pyridyl)-1,2,4-triazole

The mixture of 2 g (0.007 mol) 1-methyl-4-phenylthiosemicarbazide of isonicotinic acid and 1.2 cm^3 (0.014 mol) of chloroacetone in 20 cm^3 of methanol was heated for 5 h. The obtained solution was cooled and the formed precipitate (remained thiosemicarbazide – 0.35 g) was filtered off. The methanol filtrate was evaporated. The obtained oil was dissolved in 15 cm^3 of 2-propanol, cooled and the yellow precipitate of hydrochlorides was filtered off and dissolved in 15 cm^3 of water and neutralized with solid Na_2CO_3.

Precipitate: after crystallization from the mixture of benzene: hexane (1:1) – colourless cubes, m.p. 114–116°C, yield 0.44 g (20%) – compound II-IN.

Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 62.97%C; 4.91%H; 17.40%N.

Water filtrate: a half of the solvent was removed, the obtained precipitate was filtered off and crystallized from 2-propanol–compound III-IN.

Colourless cubes, m.p. 137–139°C, yield 0.25 g (13%).

The mixture with the compound obtained in point 4 does not show the depression of the melting point.

Analysis for the formula $C_{17}H_{16}N_4OS$:
Calculated: 62.74%C; 5.26%H, 17.21%N
Obtained: 62.47%C; 4.88%H; 16.97%N.

The 2-propanol filtrate: after removing the yellow precipitate of hydrochlorides the equal volume of water was added and the obtained solution was neutralized by solid Na_2CO_3. The formed precipitate was crystallized from the mixture of 1-propanol–water (4:1) – *mesoionic* 1-methyl-4-phenyl-3-thio-5-(4-pyridyl)-1,2,4-triazole.

Colourless quadrangle cubes, m.p. 306–308°C, yield 0.25g (16%)

The mixture with the compound obtained previously (4) does not show the depression of the melting point. UV and H-NMR spectra of those two compounds do not show differences.

7. Rearrangement of hydrochloride of α-methyl-β-(3-phenyl-4-methylthiazol-2-ylidene)-hydrazide of nicotinic acid (II-N) into hydrochloride of 2-phenylimino-3-methylnicotinoylamino-4-methyl-4-thiazoline (III-N)

1 g (0.0028 mol) of hydrochloride of compound II-N (yellow cubes, m.p. 208–210°C) was heated for 2 h in 25 cm^3 methanol saturated with HCl. The solution was removed and the residue was added with 2-propanol. The formed precipitate was filtered off and crystallized from the mixture methanol–2-propanol (1: 1).

Colourless cubes m.p. 220–222°C (dec.) was obtained; yield 0.55g (55%).

0.5 g of the obtained compound was dissolved in water and neutralized with 50% NaOH. The formed precipitate was crystallized from the mixture 2-propanol–water (1: 1).

Colourless plates, m.p. 114-116°C, yield 0.20 g (44%)

The mixtures with the compounds obtained in points 3 and 5 do not show the depression of the melting points.

Table 1. IR and H-NMR spectra of compounds II-N, II-IN, III-P, III-N and III-IN

Compound	IR C=O amide I (cm^{-1})	H-NMR [ppm]	
		Solvent	[ppm]
II-N	1615 1645*	DMSO-d6	1.75–1.76 (d, 3H, CH_3-C); 3.14 (s, 3H, CH_3-N-N=); 6.20 (d, 1H, C=CH); 7.08–7.51 (m, 6H, ar,β); 7.79–7.83 (m, 1H, γ); 8.61–8.63 (m, 2H, α)
II-IN	1626 1647*	$CDCl_3$	1.77–1.77 (d, 3H, CH_3-C); 3.28 (s, 3H, CH_3-N-N=); 5.74–5.75 (d, 1H, C=CH); 6.87–6.90 (m, 5H, ar); 7.27–7.46 (m, 2H, β); 8.59–8.61 (d, 2H, α)
III-P	1619 1677*	$CDCl_3$	2.13-2.22 (m, 3H, CH_3-C); 3.46 (s, 3H, CH_3-N-); 5.37–5.40 (m, 1H, C=CH); 6.74–7.82 (m, 8H, ar,β, γ); 8.37–8.44 (m, 1H, α)
III-N	1661 1699*	$CDCl_3$	2.13-2.15 (d, 3H, CH_3-C); 3.45 (s, 3H, CH_3-N-); 5.48–5.52 (m, 1H, C=CH); 6.86–7.39 (m, 6H, ar,β); 7.87–7.99 (m, 1H, γ) 8.63-8.77 (m, 2H, α)
III-IN	1669 1688*	$CDCl_3$	2.11-2.21 (d, 3H, CH_3-C); 3.44 (s, 3H, CH_3-N); 5.47–5.49 (d, 1H, C=CH); 6.88–7.46 (m, 7H, ar,β); 8.61–8.66 (d, 2H, α)

*Values obtained for the hydrochlorides of the studied compounds

The hydrochloride of α-methyl-β-(3-phenyl-4-methylthiazol-2-ylidene)-hydrazide of isonicotinic acid (II-IN) does not subject to such rearrangement into III-IN.

The hydrochlorides of both II-N and III-N heated in 15% HCl subject to hydrolysis and the following rearrangement to the hydrochloride of 2-phenylimino-3-methylamino-4-methyl-4-thiazoline.

The mixtures of the products of hydrolysis of II-N and II-IN with the compound obtained in point 1 does not show the depression of the melting point.

SPECTROPHOTOMETRICAL MEASUREMENTS

The basic solutions of the studied compounds were prepared by the dissolution of the weighted sample in methanol. The concentrations of those solutions were:
10^{-3} mol · dm^{-3} for III-P ; $2.0 \cdot 10^{-3}$ mol · dm^{-3} for III-N ; $2.5 \cdot 10^{-3}$ mol · dm^{-3} for III-IN;
$4.0 \cdot 10^{-3}$ mol · dm^{-3} for II-N and II-IN.

The work solutions in 20% (v/v) methanol were prepared by the dilution of the basic solutions with the proper amount of water or water and methanol. Their concentrations were established as:

II-N - $4.0 \cdot 10^{-4}$ mol · dm^{-3} for pK_1 and $8.0 \cdot 10^{-4}$ mol · dm^{-3} for pK_2 measurement
II-IN - $8.0 \cdot 10^{-4}$ mol · dm^{-3} for pK_1 and pK_2 measurement
III-P - 10^{-4} mol · dm^{-3} for pK_1 and $2.0 \cdot 10^{-4}$ mol · dm^{-3} for pK_2 measurement
III-N - $3.0 \cdot 10^{-4}$ mol · dm^{-3} for pK_1 and pK_2 measurement
III-IN - $2.0 \cdot 10^{-4}$ mol · dm^{-3} for pK_1 and pK_2 measurement.

For each compound the measurement series of solutions with the stable concentration and different pH was prepared. Methanol content was established as 2% (v/v). The concentrations were established as follows:
II-N - $4.0 \cdot 10^{-5}$ mol · dm^{-3} for pK_1 and $8.0 \cdot 10^{-5}$ mol · dm^{-3} for pK_2 measurement
II-IN - $8.0 \cdot 10^{-5}$ mol · dm^{-3} for pK_1 and pK_2 measurement
III-P - 10^{-5} mol · dm^{-3} for pK_1 and $2.0 \cdot 10^{-5}$ mol · dm^{-3} for pK_2 measurement
III-N - $3.0 \cdot 10^{-5}$ mol · dm^{-3} for pK_1 and pK_2 measurement
III-IN - $2.0 \cdot 10^{-5}$ mol · dm^{-3} for pK_1 and pK_2 measurement.

For the solutions of the measurement series the pH values and the absorption spectra from 220 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 2 and Table 3.

Table 2. The dissociation constants of compounds II-N and III-IN

Compound	Reaction	λ_{anal} [nm]	pK
II-N	$LH_2^{2+} = LH^+ + H^+$	313	1.98 ± 0.15
	$LH^+ = L + H^+$	348	3.52 ± 0.15
II-IN	$LH_2^{2+} = LH^+ + H^+$	335	1.90 ± 0.15
	$LH^+ = L + H^+$	352	3.72 ±0.10

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

Compound	Reaction	λ_{anal} [nm]	pK
III-P	$LH_2^{2+} = LH^+ + H^+$		< 1
	$LH^+ = L + H^+$	271	4.06 ± 0.03
III-N	$LH_2^{2+} = LH^+ + H^+$	279	1,77 ± 0.15
	$LH^+ = L + H^+$	269	3.65 ± 0.15
III-IN	$LH_2^{2+} = LH^+ + H^+$		1.0–2.0
	$LH^+ = L + H^+$		3.0–4.5

RESULTS

The pK_1 values are connected with the dissociation of the dication forms. It should be noticed that similarly as in the case of previously studied compounds (1, 3) the derivative of picolinic acid shows the significantly higher pK_1 value (less than 1) in comparison to the respective derivatives of nicotinic and isonicotinic acids (Table 3). The pK_2 values are related to the dissociation of monocation forms. This process occurs at pH within the range 3.0–4.5 (Table 2 and Table 3). It was not possible to measure the pK values for the compound III-IN. We determined only the ranges they are kept within (Table 3). The spectra of the studied compounds in methanol solutions were also presented (Fig. 1).

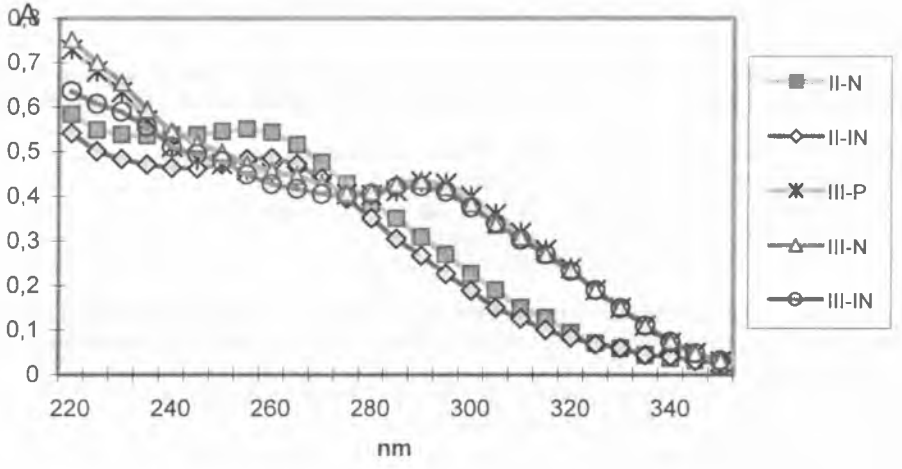


Fig.1. The spectra of the compounds II-N, II-IN, III-P, III-N, III-IN in methanol solutions

DISCUSSION

The comparison of the obtained pK values shows that there is the significant difference between the pK_1 value of the 2-phenylimino-3-methylpicolinoylamino-4-phenyl-4-thiazoline (III-P) and those obtained for the respective derivatives of nicotinic (III-N) and isonicotinic (III-IN) acids. In the case of the previously studied compounds we observed the similar phenomenon (1, 3), although concerning the compounds having different structure. Such outcomes could be assumed to prove the existence of any kind of interaction occurring in the hydrazides or amides of picolinic acid. Such interaction would result in the unexpected stability of the monocation forms and the high values of pK_1 – the binding of H^+ by the monocation would require the destruction of the stabilizing interaction and could occur only in the presence of the high concentration of H^+ (significant lower pH value). Regarding the presented observations we suggest that the monocation's forming is related to the binding of the H^+ ion by the N^3 atom of the thiazoline ring of the neutral molecule. The dication is formed as a result of the consecutive addition of H^+ to the nitrogen atom of the pyridine ring.

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SUMMARY

The α-methyl-β-(3-phenyl-4-methylthiazol-2-ylidene)-hydrazides of nicotinic (II-N) and isonicotinic (II-IN) acids as well as 2-phenylimino-3-methylpicolinoylamino-4-phenyl-4-thiazoline (III-P), 2-phenylimino-3-methylnicotinoylamino-4-phenyl-4-thiazoline (III-N) and 2-phenylimino-3-methylisonicotinoylamino-4-phenyl-4-thiazoline (III-IN) were obtained and their ionization constants were determined spectrophotometrically in aqueous solutions:
The spectra of the studied compounds in methanol solutions were also presented.

II-N	$pK_1 = 1.98 \pm 0.15$	$pK_2 = 3.52 \pm 0.15$
II-IN	$pK_1 = 1.90 \pm 0.15$	$pK_2 = 3.72 \pm 0.10$.
III-P	$pK_1 < 1$	$pK_2 = 4.06 \pm 0.03$
III-N	$pK_1 = 1.77 \pm 0.15$	$pK_2 = 3.65 \pm 0.15$
III-IN	pK_1 within the range 1.0–2.0	pK_2 within the range 3.0–4.5.

Stałe jonizacji 3-fenyloimino3-metylopirydoiloamino-4-fenylo-4-tiazolin i α-metylo-β-(3-fenylo-4-metylotiazol-2-ilideno)-hydrazydów kwasu nikotynowego i izonikotynowego

Przeprowadzono syntezę: α-metylo-β-(3-fenylo-4-metylotiazol-2-ilideno)-hydrazydu kwasu nikotynowego (II-N) i izonikotynowego (II-IN) oraz 2-fenyloimino-3-pikolinoilometyloamino-4-fenylo-4-tiazoliny (III-P), 2-fenyloimino-3- nikotynoilometyloamino-4-fenylo-4-tiazoliny (III-N) i 2-fenyloimino-3- izonikotynoilometyloamino-4-fenylo-4-tiazoliny (III-IN), a następnie wyznaczono ich stałe dysocjacji metodą spektrofotometryczną w środowisku wodnym:

II-N	$pK_1 = 1.90 \pm 0.15$	$pK_2 = 3.72 \pm 0.10$
II-IN	$pK_1 = 1.98 \pm 0.10$	$pK_2 = 4.06 \pm 0.10$.
III-P	$pK_1 < 1$	$pK_2 = 4.06 \pm 0.03$
III-N	$pK_1 = 1.77 \pm 0.15$	$pK_2 = 3.65 \pm 0.15$
III-IN	pK_1 w zakresie 1.0–2.0	pK_2 w zakresie 3.0–4.5.

Przedstawiono również widma badanych związków w roztworach metanolowych.