SYNTHESIS OF 3-(N-R)CARBAMOYL-5-(PYRID-4'-YL)PYRIDINE-2(1H)-THIONES AND THEIR DERIVATIVES

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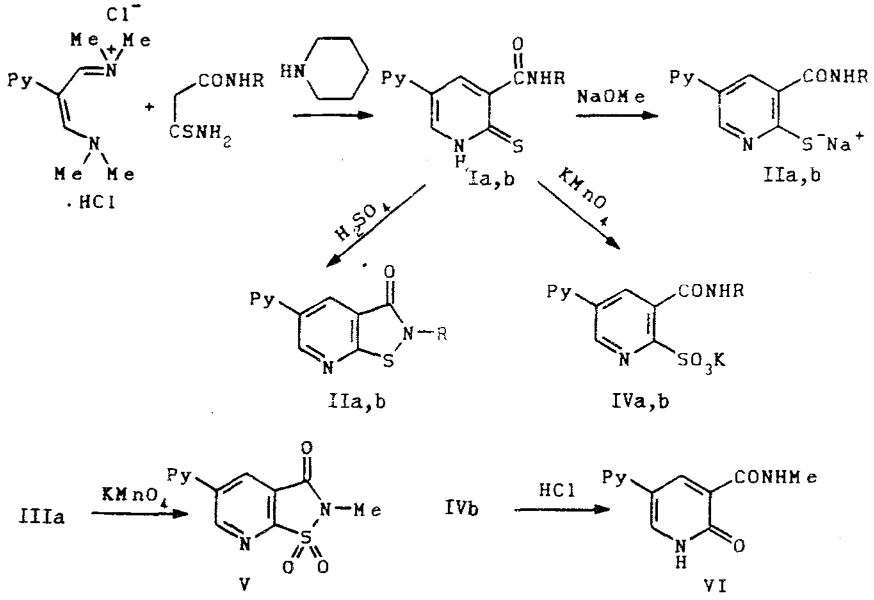
The condensation of salts of amidinium vinylogs with N-R-thiocarbamoylacetamides gave 3-(N-R)carbamoyl-5-(pyrid-4'-yl)pyridine-2(1H)-thiones, which undergo oxidative cyclization in concentrated sulfuric acid with the formation of 3-oxo-5-(pyrid-4'-yl)isothiazolo[5,4-b]pyridines. The oxidation and alkylation of the compounds referred to were investigated.

In the continuation of work on the synthesis and the study of the properties of pyridine-2(1H)-thiones [1-4], we synthesized 5-(pyrid-4'-yl)-substituted 3-(N-R)carbamoylpyridine-2(1H)-thiones, which are derivatives of the thioanalog of the known preparation amrinon [5], and products of their S-oxidation and S-alkylation.

To achieve the set objective, the hydrochloride of N,N-dimethyl-N-[3-dimethylamino-2-(pyrid-4'-yl)prop-2-enylidene]-ammonium chloride (the salt of the vinylog of amidinium) [6] was utilized as the carbonyl component in the Knoevenagel reaction, and thiocarbamoylacetamide and N-methylthiocarbamoylacetamide were utilized as the methylene component [7]. The best yields were achieved by the boiling of the initial substances in the presence of a small excess of piperidine for 30 min-2 h. The application of aqueous ammonia instead of piperidine leads to the formation of a complex mixture of products. In the case of a stronger base — sodium methoxide — the partial decomposition of the thiocarbamoylacetamides occurs with the isolation of hydrogen sulfide; this lowers the yield of the desired product significantly.



I—IV a R=H, b R=Me; a, b Py= pyrid-4-yl

The pyridine-2(1H)-thiones (Ia, b) are acidic compounds; this permits the isolation of the corresponding sodium salts (IIa, b) which are soluble in water (cf. Tables 1 and 2).

When the thiones (Ia, b) are boiled in concentrated sulfuric acid, oxidative cyclization occurs with the formation of the 3-oxo-5-(pyrid-4'-yl)isothiazolo[5, 4-b]pyridines (IIIa, b).

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TABLE 1. Characteristics of the Synthesized Compounds (I)-(X)

Compound	Empirical formula	mp, °C	IR spectra, ν, cm^{-1}		Yield, %
			C=O	NH, NH_2, OH	
Ia	$C_{11}H_9N_3OS$	272...276	1670	3075, 3202	71
Ib	$C_{12}H_{11}N_3OS$	240...243	1646	3098, 3126, 3158	72
IIa	$C_{11}H_8N_3NaOS$	338...340	1660	3036, 3212	75
IIb	$C_{12}H_{10}N_3NaOS$	316...320	1626, 1640	3052, 3172, 3342	69
IIIa	$C_{11}H_7N_3OS$	323...325	1638, 1680	3080	68
IIIb	$C_{12}H_9N_3OS$	227...228	1662	—	70
IVa	$C_{11}H_8KN_3O_4S$	>250 decomp.	1642, 1672	3060, 3098, 3168, 3328	62
IVb	$C_{12}H_{10}KN_3O_4S$	216...219	1638, 1654	3094, 3286, 3326, 3394, 3466	70
V	$C_{12}H_9N_3O_3S$	274...276	1737	—	7
VI	$C_{12}H_{11}N_3O_2$	265...268	1650, 1676	3120, 3120, 3156, 3210	65
VII	$C_{13}H_{12}N_4O_2S$	210...212	1666, 1686 shoulder	3174, 3302, 3412	82
VIII	$C_{15}H_{16}N_5O_3S$	226...230 decomp.	1662 shoulder, 1668, 1688	3180, 3320 shoulder, 3366	30
IX	$C_{13}H_{12}N_4O_4S$	254...256	1686, 1710	3174, 3360, 3444	33
X	$C_{13}H_9N_3O_2S$	275...278 decomp.	1696 shoulder, 1704	3308, 3392, 3616	73

TABLE 2. PMR Spectra of the Compounds Synthesized

Compound	Chemical shifts, δ, ppm						
	N_1H, s	NH_2 or NH, s or q	5-C_5H_4N, d d and d d	C(4)-H, d	C(6)H, d	N-CH_3, d	S-CH_2, s
Ia	14,49	8,77 and 8.53	8,81 and 8,17	9,63	7,99	—	—
Ib	14,50	10,29	8,60 and 7,72	8,72	8,38	2,85	—
IIa	—	11,83	8,43 and 7,53	8,49	7,30	—	—
IIb	—	11,27	7,72 and 6,86	7.68	7,62	2,53	—
IIIa	—	8,34	8,62 and 7,82	8,88	8,44	—	—
IIIb	—	—	8,70 and 7,88	9,27	8,60	3,38	—
IVa	—	8,50 and 7.28	8,64 and 7,76	8,88	8.28	—	—
IVb	—	8,76	8,92 and 8,42	9.10	8,46	2,74	—
V	—	—	8,68 and 7,88	9,46	8,86	3,20	—
VI	12,92	9,52	8,53 and 7,63	8,63	8,21	2,82	—
VII	—	8,16; 7,68; 7,46 and 7.02	8,68 and 7,82	8,92	8,30	—	3.76
VIII*	—	8,18; 8,04; 7,78; 7,68; 7,48 and 7,06	8,98 and 8,62	9,18	8,54	—	3,80
IX	—	7,96; 7,80; 7,62 and 7.36	8,72 and 7,86	9,16	8,40	—	4.48
X**	—	7,8	8,70 and 7,78	9,04	8,70	—	—

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*The chemical shift of the N^+—CH_2 protons at 5.36 ppm.

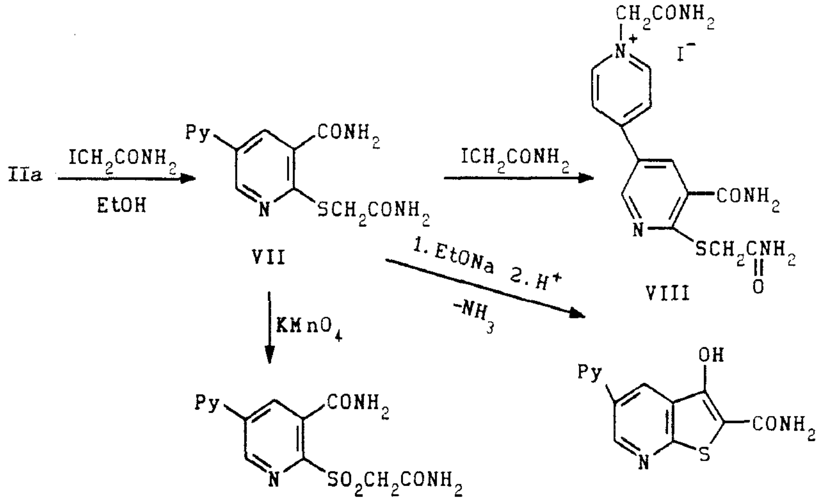
**The OH signal is strongly broadened.

The oxidation of the pyridine-2(1H)-thiones (Ia, b) and the isothiazolo[5, 4-b]pyridine (IIIb) with potassium permanganate gives the potassium salts of the pyridine-2-sulfonic acids (IVa, b) and the isothiazolo[5, 4-b]pyridine-1,1-dioxide (V) correspondingly. The compound (IVb) does not undergo cyclization in concentrated H_2SO_4 to the dioxide (V), similarly to the thione (Ib), but it is hydrolyzed to the 3-(N-methylcarbamoyl)pyridine-2(1H)-one (VI). The last is formed with a higher yield by boiling the compound (IVb) in concentrated HCl.

The alkylation of the salt (IIa) with the equimolar amount of iodoacetamide by heating the mixture briefly in ethanol leads to the formation of the 2-carbamoylmethylthiopyridine (VII). The further alkylation of compound (VII) with iodoacetamide by the brief heating of the mixture in DMF gives the 2-carbamoylmethylthio-5-(N-carbamoylmethylpyrid-4′-yl)pyridine iodide (VIII).

When the pyridine (VII) is oxidized by potassium permanganate, the corresponding 2-carbamoylsulfonylpyridine (IX) is formed.

The cyclization of the 2-carbamoylmethylthio-3-carbamoylpyridine (VII) in an alkaline medium and subsequent neutralization gives the 3-hydroxy-2-carbamoylthieno[2, 3-b]pyridine (X).



The IR spectra of the compounds (Ia, b), (IIa, b), (IVa, b), and (VI) show characteristic absorptions of the stretching vibrations of the 3-carbamoyl group at 1626-1676 cm^{-1}, and the ν_{CO} of the 3-carbamoyl and 2-carbomoylmethylthio(sulfonyl) groups is observed at 1666-1710 cm^{-1} in the case of the compounds (VII)-(X). The stretching vibrations of the 3-carbamoyl groups of the compounds (IIIa, b) and (V) increase by comparison with the analogous values of the compounds (Ia, b) and (IVa, b), reaching 1662-1680 and 1735 cm^{-1}, respectively.

The chemical shifts of the $C_{(4)}$—H and $C_{(6)}$—H protons are most characteristic of the PMR spectra of the compounds (I)-(X); the signals appear as doublets. In agreement with the work [8], the signals displaced to lower fields are assigned to the $C_{(4)}$—H proton.

EXPERIMENTAL

The IR spectra were recorded on the Perkin—Elmer 580 B instrument using mineral oil. The PMR spectra were recorded on the WH 90/DC instrument (90 MHz) in DMSO-D_6; the internal standard was TMS. The monitoring of the course of the reaction and the discreteness of the substances was accomplished using TLC on plates of Silufol UV-254; the eluent was the 15:8:1 mixture of chloroform—ethanol—aqueous ammonia.

The data of the elemental analysis of the compounds (I)-(X) for C, H, N, and S correspond with the calculated data.

3-(N-R)-Carbamoyl-5-(pyrid-4′-yl)pyridine-2(1H)-thiones (Ia, b). The mixture of 10 mmoles of the hydrochloride of N,N-dimethyl-N-[3-dimethylamino-2-(pyrid-4′-yl)prop-2-enylidene]-ammonium chloride and 10 mmoles of the N-R-thiocarbamoylacetamide in 30-40 ml of absolute ethanol and 1.2-1.5 ml of piperidine is heated for 0.5-2 h on a water bath. The reaction mixture is cooled to 5°C [20 ml of water are added in the case of the thione (Ib)], prior to the neutralization with 1 N HCl to the pH 6-7. The residue is filtered off and washed with ethanol and water. The compounds (Ia, b) are obtained with the yield of 71-72%.

3-Carbamoyl-5-(pyrid-4′-yl)pyridine-2-thiolate Sodium (IIa). The mixture of 2.31 g (10 mmoles) of the compound (Ia) in 12 ml of 1 N sodium methoxide, prepared from 0.28 g of Na and 12 ml of methanol, and 5 ml of water is boiled for 5 min on a water bath; the mixture is filtered prior to the addition of 30 ml of ethanol. The reaction mixture is cooled to 0°C, and the residue is filtered off and washed with 10 ml of ethanol. The yield of 1.9 g (75%) of the salt (IIa) is obtained.

3-(N-Methyl)-carbamoyl-5-(pyrid-4′-yl)pyridine-2-thiolate Sodium (IIb). The thione (Ib) (1.28 g; 5 mmoles) in 15 ml of 0.5 N sodium methoxide is heated for 1 min on a water bath. After filtration, 30 ml of ether are added to the solution. The reaction mixture is cooled to 0°C, and the residue is filtered off. The yield of 0.92 g (69%) of the salt (IIb) is obtained.

2-R-Oxo-5-(pyrid-4′-yl)isothiazolo[5, 4-b]pyridines (IIIa, b). The thiones (Ia, b) (10 mmoles) are heated in 10 ml of concentrated H_2SO_4 for 1 h on a water bath. The mixture is cooled and poured onto 100 ml of ice water prior to neutralization with ammonia to the pH 6. The residue is filtered off and washed with 50 ml of water and 20 ml of ethanol. The compounds (IIIa, b) are obtained with the yield of 68-70%.

Potassium Salts of 3-(N-R)-Carbamoyl-5-(pyrid-4′-yl)pyridine-2-sulfonic Acids (IVa, b). To the suspension of 5 mmoles of the thiones (Ia, b) in 50 ml of water at 20°C are added, dropwise, 1.58 g (10 mmoles) of $KMnO_4$ in 100 ml of water. After 30 min, the MnO_2 is filtered off, and the aqueous solution is concentrated to dryness. The residue is washed with 50 ml of hot ethanol. The compounds (IVa, b) are obtained with the yield of 62-70%.

3-Oxo-2-methyl-5-(pyrid-4′-yl)isothiazolo[5, 4-b]pyridine-1,1-dioxide (V). To the solution of 1.22 g (5 mmoles) of the isothiazolo[5, 4-b]pyridine (IIIb) in 50 ml of acetic acid are added, dropwise at 20°C, 1.58 g (10 mmoles) of $KMnO_4$ in 50 ml of water. After 1 h, the reaction mixture is decolorized with an aqueous solution of Na_2SO_3, neutralized with 3 N NaOH, and extracted with 3 × 20 ml of chloroform. The organic phase is concentrated, and the residue is recrystallized from water. The yield of 0.12 g (7%) of compound (V) is obtained.

3-(N-Methylcarbamoyl)-5-(pyrid-4′-yl)pyridine-2(1H)-one (VI). The mixture of 0.34 g (1 mmole) of the potassium salt of the sulfonic acid (IVb) and 5 ml of concentrated HCl is heated for 2 h on a water bath. After the cooling of the reaction mixture, 20 ml of water are added prior to the neutralization with 3 N KOH. The residue is filtered off and washed with water. The yield of 0.15 g (68%) of compound (VI) is obtained.

2-Carbamoylmethylthio-3-carbamoyl-5-(pyrid-4′-yl)pyridine (VII). The mixture of 2.5 g (10 mmoles) of the salt (IIa) and 2.22 g (12 mmoles) of iodoacetamide in 25 ml of absolute ethanol is heated to boiling and stirred for 2 h at 20°C. The residue is filtered off and washed with 20 ml of ethanol and 20 ml of water. The yield of 2.36 g (82%) of compound (VII) is obtained.

2-Carbamoylmethylthio-3-carbamoyl-5-(N-carbamoylmethyl-pyrid-4′-yl)pyridine Iodide (VIII). The mixture of 1.44 g (5 mmoles) of compound (VII) and 1.11 g (6 mmoles) of iodoacetamide in 10 ml of DMF is boiled for 3 min on a water bath and filtered. Ethanol (20 ml) is added, and the mixture is cooled to 0°C. The residue is filtered off after 24 h and washed with 20 ml of ethanol. The yield of 1.9 g (80%) of compound (VIII) is obtained.

2-Carbamoylmethylsulfonyl-3-carbamoyl-5-(pyrid-4′-yl)pyridine (IX). To the mixture of 1.44 g (5 mmoles) of compound (VII) in 60 ml of 50% acetic acid is added, dropwise for 30 min at 20°C, the solution of 2.0 g (12.5 mmoles) of potassium permanganate in 40 ml of water. The mixture is stirred for 2 h. An aqueous solution of Na_2SO_3 is added until the decolorization of the reaction mixture is achieved. The mixture is neutralized with 3 N KOH to pH 6-7. After 2 h, the residue is filtered off and washed with water. The yield of 0.54 g (33%) of compound (IX) is obtained.

3-Hydroxy-2-carbamoyl-5-(pyrid-4′-yl)thieno[2, 3-b]pyridine (X). The mixture of 1.44 g (5 mmoles) of compound (VII) in 25 ml of 0.2 N sodium ethoxide (prepared from 0.12 g of Na and 25 ml of ethanol) is heated for 10 min on a water bath and then filtered. The reaction mixture is cooled to 0°C and neutralized with 1 N HCl in ethanol. The residue is filtered off and washed with 20 ml of ethanol and 50 ml of water. The yield of 1.05 g (77%) of compound (X) is obtained.

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