SYNTHESIS AND TRANSFORMATION OF SOME THIOUREA DERIVATIVES

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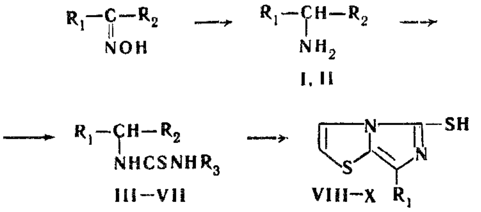
Reduction of a number of pyridylthiazolylketoximes gives amines, converted by p-ethoxyphenylisothiocyanate to the corresponding thioureas. It is shown that heating 3-pyridyl-, 4-pyridyl-, and p-$MeOC_6H_4$-2'-thiazolylmethylthiourea in dimethylformamide gives 7-substituted 5-mercaptoimidazo-[5, 1-b]thiazoles, while heating substituted 2, 4'-dipyridylmethyl-and 2-pyridyl-2'-thiazolylmethylthiourea gives 1-substituted 3-mercaptoimidazo[1, 5-a]pyridines.

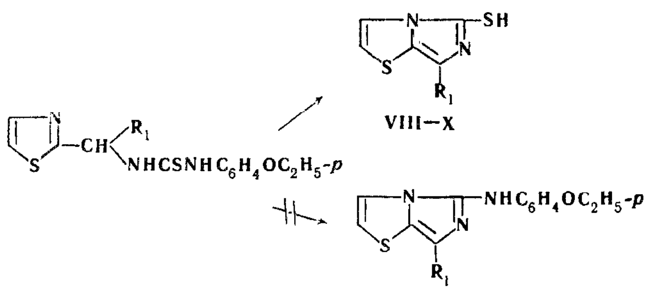
We previously prepared 2-, 3-, 4-pyridylthiazolketoximes [1]. It was of interest to reduce them to amines, and to study the properties of the latter. Zn dust in ethanolic ammonia was used to reduce the ketoximes to amines [2]. The 3- and 4-pyridyl-2-thiazolylaminomethanes (I and II respectively) were obtained in 70–75% yields, and were isolated as their hydrochloride, while the other were not obtained pure.

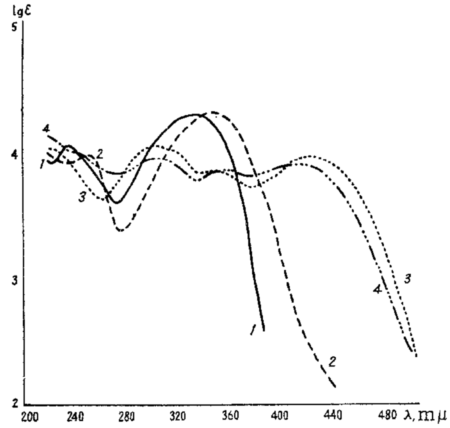
Pyridylthiazolylaminomethanes readily react with p-ethoxyphenylisothiocyanate to give the corresponding thioureas (III-VII, see table 1).



Substituted thioureas, e.g., benzothiazolylpyridylthioureas [3], undergo ring closure when heated in dimethylformamide, giving compounds with the imidazole ring condensed with a thiazole or pyridine one. The literature describes the preparation of imidazo [1, 5-a] pyridines, by treating alkylaminoalkylpyridines with phosphorus oxychloride [4]. Recently there was a synthesis of a new heterocyclic system, imidazo-[5, 1-b] thiazole, previously known only in a partly reduced from [5].

In our case formation of a condensed imidazole ring take place when substituted thioureas (III-VII) are heated in a high-boiling solvent, dimethylformamide. Reaction would be expected to proceed in two directions, with formation of 7-substituted 5-mercapto- or 5-(p-ethoxyphenylamino)imidazo [5,1-b] thiazoles:

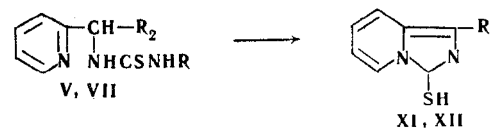




UV spectra: 1) 5-mercapto-7-(p-methoxyphenyl) imidazo [5,1-b] thiazole (X); 2) 5-mercapto-7-(3-pyridyl)imidazo [5,1-b] thiazole (VIII); 3) 1-(2-thiazolyl)-3-mercaptoimidazo [1,5-a] pyridine (XI); 4) 1-(4'-pyridyl)-3-mercaptoimidazo [1,5-a] pyridine (XII).

Elementary analysis and the presence of a mercapto group in the compounds prepared confirms that they are 7-substituted 5-mercaptoimidazo [5, 1-b] thiazoles (VIII-X) (Table 2).

Heating N-[(2, 4'-dipyridyl)methyl]-N'-p-ethoxyphenylthiourea (VII) and N-[(2-pyridyl)(2'-thiazolyl) methyl] -N'-p-ethoxyphenylthiourea (V) in dimethylformamide also leads to cyclization with imidazole ring formation. However there imidazole ring closure involves a nitrogen atom of the pyridine ring, with formation of 1-substituted and 3-mercaptoimidazo-[1, 5-a] pyridines.



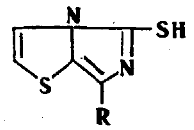
V, VI, XI R_2 = 2-thiazolyl ; VII, XII R_2 = 4-pyridyl

This is confirmed by the UV spectra of compounds XI and XII being almost identical, and differing considerably from the UV spectra of imidazo [5,1-b] thiazoles (fig.)

EXPERIMENTAL

Dihydrochloride of amino-4-pyridyl-2'-thiazolylmethane (II). 4.6 g (0.06 mole) ammonium acetate, 4.6 g (0.07 g at) Zn dust, and 220 ml aqueous ammonia were gradually added to a mixture of 4.6 g (0.022 mole) 4-pyridyl-2'-thiazolylketoxime and 55 ml 96% EtOH. The whole was heated at 78°–80° for 2 hr, then a further 1.1 g (0.017 g at) Zn dust and 40 ml aqueous ammonia added. The Zn dust and

Table 1



Compound No.	R	Mp, ° C (decomp)	Formula	Found, %				Calculated, %				Yield, %
				C	H	N	S	C	H	N	S	
VIII	3-pyridyl	240—241	$C_7H_7N_3S_2$	51.55	3.33	18.03	26.95	51.48	3.02	18.01	27.49	70
IX	4-pyridyl	273	$C_7H_7N_3S_2$	51.15	3.23	17.66	26.63	51.48	3.02	18.01	27.49	72.5
X	*p*-$CH_3OC_6H_4$	224	$C_{12}H_{10}N_2OS_2$	54.47	4.02	10.67	—	54.94	3.84	10.68	—	61

Table 2

R_1R_2>$CHNHCSNHC_6H_4OC_2H_5$-*p*

Compound No.	R_1	R_2	Mp, ° C	Formula	Found, %				Calculated, %				Yield, %
					C	H	N	S	C	H	N	S	
III	4-Pyridyl	2-Thiazolyl	135—136.5	$C_{18}H_{18}N_4OS_2$	58.42	4.89	14.78	16.83	58.35	4.90	15.12	17.31	56.3
IV	3-Pyridyl	2-Thiazolyl	149—150		58.12	4.98	15.21	17.53					85
V	2-Pyridyl	2-Thiazolyl	156—157		58.29	5.03	14.89	17.63					83.3
VI	*p*-$CH_3OC_6H_4$	2-Thiazolyl	123—124.5	$C_{20}H_{21}N_3OS_2$	60.27	4.98	10.40	15.66	60.12	5.30	10.52	16.05	54
VII	2-Pyridyl	4-Pyridyl	159—160	$C_{20}H_{20}N_4OS$	66.32	6.06	14.88	8.46	65.91	5.53	15.36	8.80	82

ammonia were added over 2 hr, 6 times in all. The reaction products were then filtered hot to remove the precipitate, which was twice washed with 50 ml hot ethanol. 25.8 g (0.65 mole) NaOH in 35 ml water was added to the cooled solution, which was then extracted with benzene and ether. The extracts were bulked, dried over $MgSO_4$, the solvents distilled off, and 3 ml dry EtOH and ethanolic HCl added to the residue (4.25 g), when the solution became dark brown, and a crystalline precipitate formed. Yield 3.8 g, colorless crystals mp 212° (ex 85% EtOH). Found: C 40.88; H 4.08; S 12.49; Cl 26.73%. Calculated for $C_9H_9N_3S \cdot 2HCl$: C 40.91; H 4.19; S 12.14; Cl 26.84%.

Dihydrochloride of amino-3-pyridyl-2'-thiazolylmethane (II). Prepared similarly to the above. Colorless crystals, mp 210°–212° (ex 96% EtOH). Found: C 40.38; H 4.07; N 15.85; S 12.45; Cl 27.52%. Calculated for $C_9H_9N_3S \cdot 2HCl$: C 40.91; H 4.19; N 15.91; S 12.14; Cl 26.84%.

N-p-Ethoxyphenyl-N'-substituted thioureas (III-VII). An equivalent quantity of p-ethoxyphenylisocyanate in dry benzene was added to a solution of the amine base in dry benzene, and the reactants refluxed for 15 min, cooled and the precipitate of thiourea filtered off and recrystallized from ethanol (see table 1).

7-Substituted 5-mercaptoimidazo[5, 1-b]thiazoles (VIII-X). The solution of the substituted thiourea III-VII was refluxed for 5 min in the minimum quantity of dimethylformamide. After cooling, the precipitate was filtered off, and recrystallized from dry EtOH (VIII), dimethylformamide (IX), or from mixed EtOH-dimethylformamide (X). It gives a reaction for the mercapto group with Na nitroprusside (see Table 2).

1-(2'-Thiazolyl)-3-mercaptoimidazo[1, 5-a]pyridine (XI). Prepared similarly to the above, yield 60%. Pale-yellow crystals mp 225°–226° (ex EtOH). Found: C 51.46; H 3.28; N 17.99; S 27.31%. Calculated for $C_{10}H_7N_3S_2$. C 51.48; H 3.02; N 18.01; S 27.49%. It gives a reaction for the mercapto group with Na nitroprusside.

p-Methoxyphenyl-2-thiazolylketone. Prepared similarly to 4-pyridyl-2-thiazolylketone [1] from an ether solution of anisic acid and 2-bromothiazole, yield 48.5%. Colorless crystals, mp 73°–74.5° (ex EtOH+ether). Found: C 60.16; H 4.07; N 6.55; S 14.92%. Calculated for $C_{11}H_9NO_2S$: C 60.27; H 4.14; N 6.39; S 14.63%.

In addition to the p-methoxyphenyl-2-thiazolylketone, p-methoxyphenylidi(2-thiazolyl)carbinol was isolated from the reaction products in 7.8% yield. Colorless crystals mp 110°–112° (ex EtOH). Found: C 55.35; H 4.09; N 9.20; S 21.03%. Calculated for $C_{14}H_{12}N_2O_2S_2$: C 55.24; H 3.97; N 9.20; S 21.07%.

p-Methoxyphenyl-2-thiazolylketoxime. Prepared by heating an ethanol solution of the appropriate ketone with hydroxylamine hydrochloride in the presence of pyridine, yield 87.5%. Colorless crystals mp 160°–162° (ex 50% EtOH). Found: C 56.95; H 4.19; N 11.34; S 13.93%. Calculated for $C_{11}H_{10}N_2O_2S$: C 56.40; H 4.30; N 11.96; S 13.69%.

1-(4'-Pyridyl)-3-mercaptoimidazo[1, 5-a]pyridine (XII). Prepared similarly to 5-mercapto-7-pyridylimidazo[1, 5-b]thiazoles, in 72% yield. Orange-brown crystals, decomp 246°–248° (ex dry EtOH). Found: C 63.43; H 4.13; S 14.24%. Calculated for $C_{12}H_9N_3S$: C 63.41; H 3.99; S 14.11%.

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