ISSN 1070-3632, Russian Journal of General Chemistry, 2012, Vol. 82, No. 11, pp. 1869–1872. © Pleiades Publishing, Ltd., 2012.
Original Russian Text © A.P. Gulea, K.S. Lozan-Tyrshu, V.I. Tsapkov, I.D. Korzha, V.F. Rudik, 2012, published in Zhurnal Obshchei Khimii, 2012, Vol. 82, No. 11, pp. 1880–1884.

Coordination Compounds of Copper with 2-Formylpyridine 4-(Dimethylphenyl)thiosemicarbazones

A. P. Gulea[a], K. S. Lozan-Tyrshu[b], V. I. Tsapkov[a], I. D. Korzha[a], and V. F. Rudik[b]

[a] *Moldova State University, ul. Mateevicha 60, Chisinau, 2009 Moldova*
e-mail: dociu1946@yahoo.com

[b] *Testemitanu Moldova State University of Medicine and Pharmacy, Chisinau, Moldova*

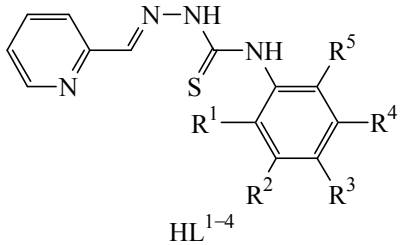
Received September 6, 2011

Abstract—2-Formylpyridine 4-(2,6-dimethylphenyl)- (HL^1), 4-(2,5-dimethylphenyl)- (HL^2), 4-(3,4-dimethylphenyl)- (HL^3), and 4-(2,4-dimethylphenyl)thiosemicarbazones (HL^4) react with copper chloride and nitrate to form coordination compounds $CuL^{1–4}X{\cdot}nH_2O$ [X = Cl^-, NO_3^-; n = 1, 2]. All compounds have a polynuclear structure. Azomethines $HL^{1–4}$ act as the bridging monodeprotonated tridentate N,N,S-ligands. The thermolysis of the complexes includes the dehydration (70–90°C) and total thermal decomposition (350–520°C). The complexes synthesized exhibit a selective antimicrobial activity against a series of standard strains of *Staphylococcus aureus* and *Escherichia coli* in the concentration range of 0.009–37.5 μg ml^{-1}.

DOI: 10.1134/S1070363212110242

The thiosemicarbazide derivatives are widely used in medicine for the treatment of various diseases [1, 2]. All of them have a large set of the electron-donor atoms and react with a variety of metal ions to form versatile coordination compounds [3–5]. Many of these compounds are biologically active [6–8]. They can be used as a basis for the preparation of selectively acting microbiological culture media, as well as the potential disinfectants and antiseptics. Therefore, the synthesis and study of the new coordination compounds of the biometals with thiosemicarbazones is of both scientific and practical interest.

The purpose of this work is the synthesis of the copper complexes with 2-formylpyridine 4-(2,6-dimethylphenyl)- (HL^1), 4-(2,5-dimethylphenyl)- (HL^2), 4-(3,4-dimethylphenyl)- (HL^3), and 4-(2,4-dimethylphenyl)thiosemicarbazones (HL^4) and the study of their composition, structure, and physicochemical properties.



$HL^{1–4}$

HL^1: $R^1 = R^5 = CH_3$, $R^2 = R^3 = R^4 = H$; HL^2: $R^2 = R^5 = CH_3$, $R^1 = R^3 = R^4 = H$; HL^3: $R^2 = R^3 = CH_3$, $R^1 = R^4 = R^5 = H$; HL^4: $R^1 = R^3 = CH_3$, $R^2 = R^4 = R^5 = H$.

The reactions of copper chlorides and nitrates in hot ethanol solutions, 50–55°C, with thiosemicarbazones $HL^{1–4}$ taken in an equimolar ratio yield the fine-crystalline substances **I–VI** of general formula $Cu(L^{1–4})X{\cdot}nH_2O$ [$HL^{1–4}$ = HL^1 (**I, II**), HL^2 (**III, IV**), HL^3 (**V**), HL^4 (**VI**); X = Cl (**I, III**), NO_3 (**II, IV–VI**); n = 1 (**II**), 2 (**I, III–VI**)]. The resulting coordination compounds **I–VI** are insoluble in diethyl ether, poorly soluble in water and alcohol, soluble in dimethylformamide (DMF), dimethyl sulfoxide, and acetonitrile. Their yields and physicochemical characteristics are given in Table 1.

The elemental and thermal analysis, molar conductivity measuring, IR spectroscopy, and magnetochemistry methods were used to establish the identity of composition and structure of the complexes obtained.

According to the molar conductivity data in DMF all the compounds synthesized are non-electrolytes (æ = 2–6 Ω^{-1} cm^2 mol^{-1}).

The magnetic data of the complexes **I–VI** (Table 1) shows that they have a polynuclear structure, since the values of the effective magnetic moments are reduced in comparison with the spin only value for one unpaired electron (μ_{eff} 0.90–1.10 BM).

Table 1. Physicochemical characteristics of copper complexes with 2-formylpyridine 4-dimethylphenyl)thiosemicarbasones

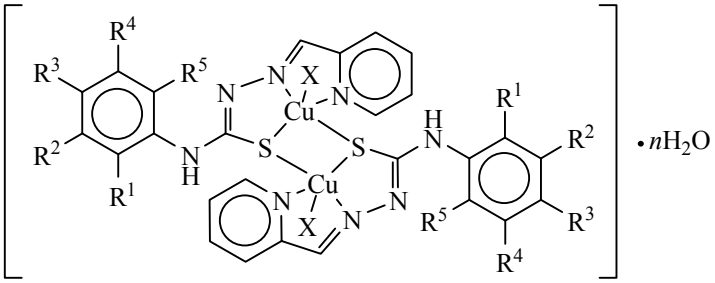
Comp. no.	Yield, %	μ_{eff},[a] BM	æ,[a] Ω^{-1} cm^2 mol^{-1}	Found, %			Formula	Calculated, %			T_{decomp}, °C
				Cu	N	S		Cu	N	S	
I	70	0.94	2	15.01	13.17	7.41	$C_{15}H_{19}ClCuN_4O_2S$	15.29	13.38	7.65	520
II	64	1.04	6	14.27	15.54	6.90	$C_{15}H_{19}CuN_5O_5S$	14.38	15.73	7.19	370
III	72	0.91	3	16.09	13.77	8.19	$C_{15}H_{17}ClCuN_4OS$	15.98	13.99	7.99	485
IV	68	0.90	5	14.11	15.57	7.01	$C_{15}H_{19}CuN_5O_5S$	14.38	15.73	7.19	360
V	67	0.97	4	14.19	15.46	6.92	$C_{15}H_{19}CuN_5O_5S$	14.38	15.73	7.19	350
VI	70	1.10	6	14.44	15.61	6.90	$C_{15}H_{19}CuN_5O_5S$	14.38	15.73	7.19	360

[a] At 294 K.

In keeping with the thermal analysis data (Table 1), the thermolysis of compounds **I–VI** proceeds in two stages. The DTA curves of all the complexes show an endothermic effect in the range of 70–90°C corresponding to the dehydration process. The subsequent exothermic effect on the DTA curves observed in the range of 350–520°C is associated with the thermal oxidative destruction of the coordinated thiosemicarbazones $HL^{1–4}$. The temperature of the complete decomposition (T_{decomp}) of a substance depends on the nature of the inner-sphere ligands, and it increases when the nitrate ion was replaced with the chloride ion. At the same acido ligand the T_{decomp} value varies in the series: $HL^1 > HL^2 \approx HL^4 > HL^3$.

To determine the coordination way of the ligands to the central ion, we performed a comparative analysis of IR spectra of the synthesized complexes **I–VI**, initial thiosemicarbazones $HL^{1–4}$, as well as the spectra described in [5] for the coordination compounds of copper chloride and nitrate with 2-formylpyridine thiosemicarbazone whose structures were determined by the XRD analysis (Table 2). The azomethines $HL^{1–4}$ were found to be the tridentate *N*,*N*,*S*-ligands. They coordinate to the ion-complexing agents via the pyridine and azomethine nitrogen atoms and also via the sulfur atom to form two five-membered metallocycles. This fact is also confirmed by the disappearance of the absorption bands ν(NH) and ν(C=S) in the IR spectra of the complexes, which are observed at 1540–1535 and 1125–1120 cm^{-1}, respectively, in the IR spectra of the starting thiosemicarbazide. In addition, the IR spectra of the complexes contain the absorption band ν(C–S) in the range of 750–740 cm^{-1}. The ν(C=N) absorption band contains two components and is shifted to shorter wavelengths compared with those in the spectrum of thiosemicarbazone. The absorption band in the range of 1570–1560 cm^{-1} was attributed to the stretching vibrations of the fragment >C=N–N=C< [7–10]. This character of the spectra indicates the enolization of thiosemicarbazones during the formation of the coordination compounds **I–VI**. The IR spectra of all complexes contain new absorption bands at 530–405 [ν(Cu–N)] and 450–440 cm^{-1} [ν(Cu–S)]. The involvement of the other functional groups of $HL^{1–4}$ into the coordination with the central ion is excluded because their characteristic absorption bands appear in the same ranges as in the spectra of the original thiosemicarbazones.

The resulting physicochemical data allow us to represent the distribution of the chemical bonds in the complexes **I–VI** as follows.



$\cdot nH_2O$

R^1 = H, CH_3; R^2 = H, CH_3; R^3 = H, CH_3; R^4 = H, CH_3; R^5 = H, CH_3; X = $Cl^–$, $NO_3^–$; *n* = 2, 4.

Table 2. The IR spectra parameters (cm^{-1}) of compounds HL^{1-4} and **I–VI**

Comp. no.	ν(NH)	ν(C=N)	ν(>C=N–N=C<)	δ(C–N)	ν(C=S)	ν(C–N)	ν(C–S)	ν(Cu–N), ν(Cu–S)
HL^1	1538	1625	–	1194, 1149	1125	988, 944	–	–
HL^2	1540	1620	–	1190, 1150	1120	990, 940	–	–
HL^3	1535	1625	–	1192, 1150	1120	987, 940	–	–
HL^4	1536	1620	–	1195, 1140	1124	988, 945	–	–
I	–	1590, 1585	1565	1174, 1143	–	974, 931	741	515, 443, 416
II	–	1595, 1590	1570	1175, 1140	–	975, 930	750	530, 445, 415
III	–	1590, 1585	1565	1180, 1140	–	970, 932	740	525, 452, 430
IV	–	1592, 1587	1560	1175, 1145	–	975, 935	742	520, 450, 425
V	–	1600, 1595	1565	1170, 1141	–	970, 930	745	517, 447, 420
VI	–	1595, 1588	1570	1175, 1140	–	970, 931	744	525, 450, 415

Table 3. Minimal inhibitory (MIC) and bactericidal (MBC) concentrations of **I–VI** relative to the test-microorganisms (μg ml^{-1})

Comp. no.	Gram-positive microorganisms				Gram-negative microorganisms					
	Staphylococcus aureus, ATCC 25923		*Bacillus cereus* NCTC 8035		*Escherichia coli*, ATCC 25922		*Shigela sonnei*		*Salmonella abony* NCTC 03/03	
	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC	MIC	MBC
Starting compounds[a]	>300	>300	>300	>300	>300	>300	>300	>300	>300	>300
I	0.009	0.018	0.009	0.018	9.37	37.5	0.07	0.07	9.37	9.37
II	0.58	2.34	0.58	1.17	37.5	75	0.58	0.58	37.5	75
III	0.018	0.018	0.009	0.03	9.37	18.75	0.018	0.018	9.37	9.37
IV	0.018	0.018	0.03	0.03	37.5	75	0.07	0.029	37.5	75
V	0.009	0.03	0.009	0.018	37.5	75	0.009	0.009	9.35	18.75
VI	0.009	0.009	0.018	0.018	9.37	37.5	0.009	0.009	9.37	9.37

[a] Copper(II) chloride and nitrate and thiosemicarbazones HL^{1-4}.

It has been shown in [11–13] that many thiosemicarbazone complexes with the biometals inhibit selectively the growth and reproduction of diverse kinds of microorganisms. In this regard, the antimicrobial activity of the synthesized coordination compounds **I–VI** was studied *in vitro*. The experimental data are shown in Table 3. The experimental data suggest that all original copper salts and thiosemicarbazones HL^{1-4} did not show any antimicrobial activity against the above-mentioned microorganisms, while the complexes **I–VI** possess a selective bacteriostatic and bactericidal activity against the gram-positive (in the concentration range of 0.0009–2.34 μg ml^{-1}) and gram-negative organisms (in the

concentration range of 0.009–75.0 μg ml^{-1}). The minimum inhibitory (MIC) and minimum bactericidal (MBC) concentrations of the complexes **I–VI** depend mainly on the nature of the acido ligand and the position of the substituents (R) in the azomethines HL^{1-4}: when the substituents are similar the MIC and MBC values vary in the series: $Cl^- > NO_3^-$ and $HL^4 \geq HL^3 > HL^2 > HL^1$. In addition, the closeness of the MIC and MBC values for many compounds indicates the bactericidal character of their action.

The above experimental data indicate that further search for the antimicrobial substances among the thiosemicarbazones coordination compounds with biometals is promising.

EXPERIMENTAL

The molar conductivity of DMF solutions of complexes **I–VI** (20°C, *c* 0.001 mol l^{-1}) was measured on a P-38 slide-wire bridge. The IR spectra of the substances preliminary dried at 105°C to constant weight were recorded on a Specord M-80 spectrometer (from mulls in mineral oil). The effective magnetic moments of compounds **I–VI** were determined by the Gouy method. The calculation of the molar magnetic susceptibility corrected for the diamagnetism was made by the theoretical values of the magnetic susceptibility of organic compounds. The DT and TG analysis was performed on a Paulik–Paulik–Erdey derivatograph in the range of 20–1000°C in air relative to Al_2O_3 (corundum crucible).

The starting 4-(2,6-dimethylphenyl)- (mp 210–212°C), 4-(2,5-dimethylphenyl)- (mp 188–191°C), 4-(3,4-dimethylphenyl)- (mp 197–200°C), and 4-(2,4-dimethylphenyl)thiosemicarbazone (mp 204–206°C) of 2-formylpyridine were prepared as in [13].

The antimicrobial activity was studied *in vitro* by the method of double serial dilutions in liquid medium (meat-peptone broth, pH 7.0) by the standard procedure [14].

Di(μ-*S*)-bis{chloro-[2-picolidene-4-(2,6-dimethylphenyl)thiosemicarbazido]copper} tetrahydrate (I). To 10 mmol of 2-formylpyridine 4-(2,6-dimethylphenyl)thiosemicarbazone solution in 50 ml of ethanol was added a 10 mmol of copper(II) chloride dihydrate solution in 20 ml of ethanol under stirring at 50–55°C. The reaction mixture was refluxed for 50–60 min. After cooling to room temperature, the solvent was slowly evaporated. The dark green residue was filtered off on a glass frit filter, washed with a small amount of alcohol, diethyl ether, and dried in air to the constant weight.

Similarly, starting from 2-formylpyridine 4-(2,6-dimethylphenyl)-, 4-(2,5-dimethylphenyl)-, 4-(3,4-dimethylphenyl)- and 4-(2,4-dimethylphenyl)thiosemicarbazones and copper(II) chloride and nitrate hydrates (at molar ratio of 1:1) we synthesized compounds **II–VI**. The yields and some physicochemical characteristics of the obtained complexes **I–VI** are given in Tables 1, 2.

REFERENCES

1. Mashkovskii, M.D., *Lekarstvennye sredstva* (Drugs), Moscow: Novaya Volna, 2008.
2. Zhungietu, G.I. and Granik, V.G., *Osnovnya printsipy konstruirovaniya lekarstv* (Basic Principles of the Drug Design), Chisinau: IPK Mold. Gos. Univ., 2000.
3. Gerbeleu, N.V., Arion, V.B., and Burges, J., *Template Synthesis of Macrocyclic Compound*, Weinheim: Wiley-VCH, 1999.
4. Samus', N.M., Chumakov, Yu.M., Tapcov, V.I., Bocelli, G., Simonov, Yu.A., and Gulea, A.P., *Zh. Obshch. Khim.*, 2009, vol. 79, no. 3, p. 439.
5. Chumakov, Yu.M., Tapcov, V.I., Jeannot, E., Bayrak, N.N., Bocelli, G., Poirier, D., Roy, J., and Gulea, A.P., *Kristallografiya*, 2008, vol. 53, no. 5, p. 833.
6. Gulea, A., Poirier, D., Roy, J., Stavila, V., Bulimestru, I., Tapcov, V., Birca, M., and Popovschi, L., *J. Enzyme Inhib. Med. Chem*., 2008, vol. 23, no. 6, p. 806.
7. Gulea, A.P., Spanu, S.N., Tapcov, V.I., and Poirier, D., *Zh. Obshch. Khim.*, 2008, vol. 78, no. 5, p. 841.
8. Gulea, A.P., Prisakar, V.I., Tapcov, V.I., Buracheva, S.A., Spanu, S.N., and Bejenari, N.P., *Khim.-Farm. Zh.*, 2008, vol. 42, no. 6, p. 41.
9. Arion, V.B., Gerbeleu, N.V., and Indrichan, K.M., *Zh. Neorg. Khim.*, 1985, vol. 30, no. 1, p. 126.
10. Gulea, A.P., Prisakar, V.I.,Tapcov, V.I., Buracheva, S.A., Spanu, S.N., Bejenari, N.P., Poirier, D., and Roy, J., *Khim.-Farm. Zh.,* 2007, vol. 41, no. 11, p. 29.
11. Zelenin, K.N., Kuznetsova, O.B., Saminskaya, A.G., Alekseeva, V.V., Karimov, Z.T., Sivolodskii, E.P., Sofronov, G.A., Novikov, N.I., and Preobrazhenskaya, T.N., *Khim.-Farm. Zh.*, 1994, vol. 31, no. 2, p. 34.
12. Ovsepyan, T.R., Gabrielyan, G.E., Simonyan, G.K., Arsenyan, F.G., Stepanyan, G.M., and Garibdzhanyan, B.T., *Khim.-Farm. Zh*., 2000, vol. 34, no. 5, p. 21.
13. Johari, R.B. and Sharma, R.C., *J. Indian Chem. Soc*., 1988, no. 11, p. 793.
14. Pershin, G.N., *Metody eksperimental'noi khimioterapii* (Methods of Experimental Chemotherapy), Moscow: Meditsina, 1971, p. 357.