Russian Journal of Applied Chemistry, Vol. 77, No. 8, 2004, pp. 1321–1324. Translated from Zhurnal Prikladnoi Khimii, Vol. 77, No. 8, 2004, pp. 1336–1339.

ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Reactions of Dithiocarbamic Acids Derived from Alkaloids, Morpholine, and Piperidine with Acrylic Acid and Its Derivatices

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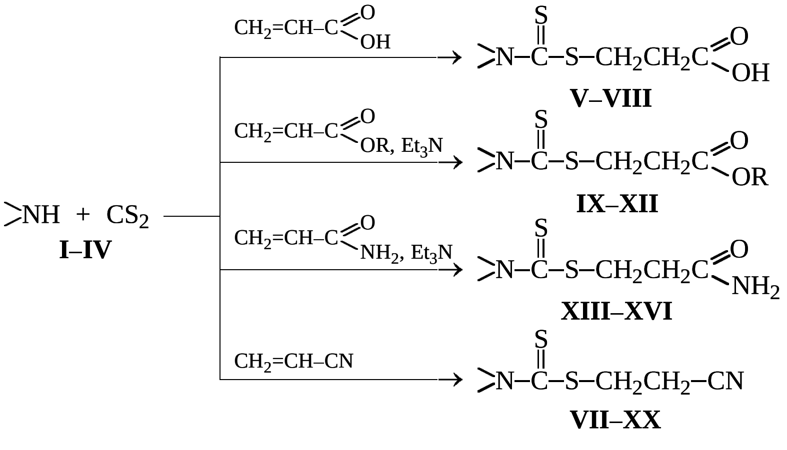
Received April 20, 2004

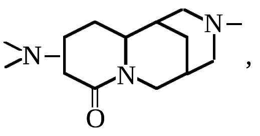
Abstract—β-(Thiocarbamoylthio)propionic acids derived from alkaloids, morpholine, and piperidine and their esters, amides, and nitriles were prepared by reactions of the corresponding dithiocarbamic acids with acrylic acid and its derivatives. Some of the compounds were tested for insecticidal activity.

Dithiocarbamic acids are important synthetic precursors of various antimicrobial [1], fungicidal [2], pesticidal [3], bactericidal [4], and other biologically active agents.

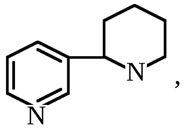
Dithiocarbamic acid esters containing various functional groups in the mercaptan residue can be prepared by reactions of dithiocarbamic acids with unsaturated electrophilic compounds in which the double bond is activated with electron-withdrawing substituents, such as unsaturated acids, their esters and anhydrides, unsaturated ketones, and related compounds.

Proceeding with a search for new biologically active dithiocarbamate derivative of alkaloids and their synthetic structural analogs [5], we performed reactions of dithiocarbamic acids prepared *in situ* from amines **I**–**IV** and CS_2 (with or without the base catalyst, triethylamine) with acrylic acid and its derivatives:

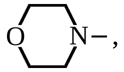




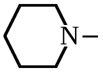
I, V, IX, XIII, XVII



II, VI, X, XIV, XVIII



III, VII, XI, XV, XIX



IV, VIII, XII, XVI, XX

R = CH_3 (**a**), *i*-C_3H_7 (**b**), and C_4H_9 (**c**).

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Table 1. Yields, physicochemical constants, and elemental analyses of **V**–**VIII**

Compound	Yield, %	mp, °C	R_f^*	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
V	89	252–253	0.58	52.61	6.46	8.32	$C_{15}H_{22}N_2O_3S_2$	52.63	6.43	8.19
VI	86	Oil	0.53	54.24	5.86	9.02	$C_{14}H_{18}N_2O_2S_2$	54.19	5.81	9.03
VII	92	120–121	0.76	40.79	5.52	6.00	$C_8H_{13}NO_3S_2$	40.85	5.53	5.96
VIII	93	106-107	0.69	46.38	6.43	6.05	$C_9H_{15}NO_2S_2$	46.35	6.44	6.01

* Eluent 2-propanol–ammonia–water, 7 : 2 : 1.

Table 2. Yields, physicochemical constants, and elemental analyses of **IX**–**XII**

Compound	Yield, %	n_D^{20} (mp, °C)	R_f^*	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
IXa	70	(94–95)	0.65	53.96	6.70	7.90	$C_{16}H_{24}N_2O_3S_2$	53.93	6.74	7.87
IXb	65	1.5359	0.58	55.59	6.21	8.68	$C_{15}H_{20}N_2O_2S_2$	55.55	6.17	8.64
IXc	73	(59–60)	0.71	43.41	6.00	5.59	$C_9H_{15}NO_3S_2$	43.37	6.02	5.62
Xa	77	1.5468	0.69	48.55	7.03	5.71	$C_{10}H_{17}NO_2S_2$	48.58	6.88	5.67
Xb	66	1.5518	0.62	56.22	7.32	7.27	$C_{18}H_{28}N_2O_3S_2$	56.25	7.29	7.29
Xc	61	1.5423	0.61	57.97	6.87	7.93	$C_{17}H_{24}N_2O_2S_2$	57.95	6.82	7.95
XIa	70	1.5585	0.75	47.70	6.83	5.01	$C_{11}H_{19}NO_3S_2$	47.65	6.86	5.05
XIb	68	1.5510	0.66	52.38	7.62	6.01	$C_{12}H_{21}NO_2S_2$	52.36	7.64	5.09
XIc	63	1.5138	0.49	57.30	7.56	7.01	$C_{19}H_{30}N_2O_3S_2$	57.29	7.54	7.04
XIIa	57	1.5265	0.36	59.03	7.13	7.68	$C_{18}H_{26}N_2O_2S_2$	59.02	7.10	7.65
XIIb	71	1.5172	0.60	51.54	6.96	4.66	$C_{13}H_{21}NO_3S_2$	51.49	6.93	4.62
XIIc	74	1.5157	0.55	54.14	7.68	4.90	$C_{13}H_{22}NO_2S_2$	54.17	7.64	4.86

* Eluent benzene–acetone, 1 : 1.

In view of the high physiological activity of dithiocarbamates and alkaloids, it seemed interesting to combine, in a single molecule, alkaloid and dithiocarbamate fragments and to study the biological properties of such compounds.

Acrylic acid contains a double bond conjugated with the carboxy group. The withdrawing effect of the carbonyl oxygen on the π electrons of the double bond facilitates its attack by nucleophilic agents. Therefore, dithiocarbamic acids react with acrylic acid under mild conditions to form the corresponding β-[alkaloido(amino)thiocarbonylthio]propionic acids **V**–**VIII** in high yields, 86–93% (Table 1).

The alkyl groups in alkyl acrylate exhibit a positive inductive effect and noticeably decrease the conjugation between the carbonyl oxygen atom and C=C bond of the acrylate; as a result, the rate of reaction of dithiocarbamic acids with alkyl acrylates somewhat decreases. Compounds **I**–**IV** react with alkyl acrylates under more severe conditions, in the presence of triethylamine, apparently via formation of an ammonium salt. The length of the carbon chain and the degree of substitution of the α-C atom in the alcoholic residue exert no significant effect on the yield of β-[alkaloido(amino)thiocarbonylthio]propionic acid esters **IX**–**XII**. The yield of esters **IX**–**XII** derived from methyl (**a**), isopropyl (**b**) and butyl (**c**) acrylates ranges from 57 to 77% (Table 2).

The reaction with acrylamide also occurs in the presence of triethylamine; the yields of β-[alkaloido(amino)thiocarbonylthio]propionic acid amides **XIII**–**XVI** range from 74 to 91% (Table 3). In the absence of triethylamine, the reaction takes somewhat more time and requires heating; the yield of amides **XIII**–**XVI** appreciably decreases. This may be caused by thermal instability of dithiocarbamates and by consumption of the amine or alkaloid as a base for the salt formation. The product of direct

Table 3. Yields, physicochemical constants, and elemental analyses of **XIII**–**XVI**

Compound	Yield, %	mp, °C	R_f^*	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
XIII	87	148–150	0.50	52.81	6.70	12.38	$C_{15}H_{23}N_3O_2S_2$	52.79	6.74	12.32
XIV	74	115–116	0.43	54.34	6.19	13.55	$C_{14}H_{19}N_3OS_2$	54.37	6.15	13.59
XV	91	140–141	0.51	40.06	6.02	12.01	$C_8H_{14}N_2O_2S_2$	41.03	5.98	11.97
XVI	78	106–107	0.54	46.51	6.87	12.11	$C_9H_{16}N_2OS_2$	46.55	6.90	12.07

[*] Eluent benzene–acetone, 1 : 1.

Table 4. Yields, physicochemical constants, and elemental analyses of **XVII**–**XX**

Compound	Yield, %	mp, °C	R_f^*	Found, %			Formula	Calculated, %		
				C	H	N		C	H	N
XVII	85	41–42	0.79	55.77	6.46	13.02	$C_{15}H_{21}N_3OS_2$	55.73	6.50	13.00
XVIII	79	Oil	0.78	57.70	5.88	14.48	$C_{14}H_{17}N_3S_2$	57.73	5.84	14.43
XIX	87	88–89	0.81	44.40	5.52	13.01	$C_8H_{12}N_2OS_2$	44.44	5.56	12.96
XX	90	78–79	0.75	50.50	6.58	13.12	$C_9H_{14}N_2S_2$	50.47	6.54	13.08

[*] Eluent benzene–acetone, 1 : 1.

addition of the amine to acrylamide is formed as a by-product.

The reactivity of acrylonitrile toward **I**–**IV** is similar to the reactivity of acrylic acid, which is due to the high electron-withdrawing power of the nitrile group, facilitating nucleophilic attack of the C=C bond by the carbamate anion. The reactions of *in situ* prepared diethyldithiocarbamic acids with acrylonitrile are performed with a small excess of CS_2; β-[alkaloido(amino)thiocarbonylthio]propionitriles **XVII**–**XX** are obtained in high yields, 78–91% (Table 4).

The nucleophilic addition of the dithiocarbamates to acrylic acid and its derivatives occurs against the Markownikoff rule [scheme (1)].

β-[Alkaloido(amino)thiocarbonylthio]propionic acids **V**–**VIII** are crystalline substances insoluble in organic solvents, but readily soluble in alkalis with the formation of the corresponding salts. Esters **IX**–**XII**, amides **XIII**–**XVI**, and nitriles **XVII**–**XX** were isolated as crystalline substances or light yellow oils, soluble in the majority of organic solvents.

Some of compounds **V**–**XX** and alkali metal salts of **V**–**VIII** were tested for insecticidal activity with respect to *Lepidosaphes ulmi* (Diaspididae family), *Capitophorus ribis* (Aphididae family), and *Abrahas grossulariata* (Geometridae family). The insecticidal activity was compared to that of a reference agent, Sumi-alpha (Sumito Chemical Co., Ltd, Japan).

We found that salts of **V** and **VIII**, sodium β-[cytisinothiocarbonylthio]propionate and potassium β-[cytisinothiocarbonylthio]propionate, exhibit pronounced insecticidal activity with respect to all of the examined pests, exceeding that of Sumi-alpha by a factor of 1.5–2.

The results were confirmed by the results of biological tests; compounds **V** and **VIII** were recommended for further comprehensive studies with the aim to assess the possibility of their use in agriculture as pesticides.

EXPERIMENTAL

The compositions and structures of the compounds were confirmed by elemental analysis and IR spectroscopy.

The IR spectra were recorded on a UR-20 spectrometer (KBr pellets, mulls in mineral oil, or solutions in $CHCl_3$ and CCl_4).

β-(Cytisinothiocarbonylthio)propionic acid V. A solution of 1.90 g (0.01 mol) of cytisine in ethanol was added to a solution of 0.76 g (0.01 mol) of CS_2 and 0.72 g (0.01 mol) of acrylic acid in ethanol.

The mixture was stirred for 5–6 h. After the removal of the solvent, a white precipitate formed. Recrystallization from alcohol gave 3.04 g (89.0%) of **V**, mp 252–253°C. IR spectrum, ν, cm^{-1}: 700–600 (C–S), 1500–1470 (N–C=S), 1320–1210 (COOH).

Found, %: C 52.61, H 6.46, N 8.32.
$C_{15}H_{22}N_2O_3S_2$.
Calculated, %: C 52.63, H 6.43, N 8.19.

Compounds **VI**–**VIII** were prepared similarly.

Methyl β-(cytisinothiocarbonylthio)propionate IXa. A solution of 1.90 g (0.01 mol) of cytisine and 1.01 g (0.01 mol) of triethylamine in ethanol was slowly added dropwise with stirring to a solution of 0.86 g (0.01 mol) of methyl acrylate and 0.76 g (0.01 mol) of CS_2 in ethanol. The mixture was heated for 1 h at 60–70°C. After the removal of the solvent, a white precipitate formed. Its recrystallization from alcohol gave 2.5 g (70.0%) of **IXa**, mp 94–95°C. IR spectrum, ν, cm^{-1}: 700–610 (C–S), 1500–1470 (N–C=S), 1410–1300 (COO^-).

Found, %: C 53.96, H 6.70, N 7.90.
$C_{16}H_{24}N_2O_3S_2$.
Calculated, %: C 53.93, H 6.74, N 7.87.

Compounds **Xa**–**XIIa**, **IXb**–**XIIb**, and **IXc**–**XIIc** were prepared similarly.

β-(Cytisinothiocarbonylthio)propionamide XIII. A solution of 1.9 g (0.01 mol) of cytisine and 1.01 g (0.01 mol) of triethylamine in ethanol was slowly added dropwise with stirring to a solution of 0.71 g (0.01 mol) of acrylamide and 0.76 g (0.01 mol) of CS_2 in absolute ethanol. The mixture was heated for 4–5 h. After the removal of the solvent, a white precipitate formed. Its recrystallization from alcohol gave 2.9 g (87.0%) of **XIII**, mp 148–150°C. IR spectrum, ν, cm^{-1}: 710–610 (C–S), 1520–1480 (N–C=S), 1140–1070 ($CONH_2$).

Found, %: C 52.81, H 6.70, N 12.38.
$C_{15}H_{23}N_3O_2S_2$.
Calculated, %: C 52.79, H 6.74, N 12.32.

Compounds **XIV**–**XVI** were prepared similarly.

β-(Cytisinothiocarbonylthio)propionitrile XVII. A solution of 1.9 g (0.01 mol) of cytisine in ethanol was slowly added dropwise to a solution of 0.53 g (0.01 mol) of acrylonitrile and 1.14 g (0.015 mol) of CS_2 in ethanol. The mixture was stirred at 40–50°C for 2–3 h. After the removal of the solvent, a light yellow oil crystallizing on storage was obtained. Its recrystallization from alcohol gave 2.75 g (85.0%) of **XVII**, mp 41–42°C. IR spectrum, ν, cm^{-1}: 700–610 (C–S), 1510–1460 (N–C=S), 2260–2240 (C≡N).

Found, %: C 55.77, H 6.46, N 13.02.
$C_{15}H_{21}N_3OS_2$.
Calculated, %: C 55.73, H 6.50, N 13.00.

Compounds **XVIII**–**XX** were prepared similarly.

CONCLUSIONS

(1) β-[Alkaloido(amino)thiocarbonylthio]propionic acids and their esters, amides, and nitriles were prepared by reactions of dithiocarbamic acids derived from alkaloids, morpholine, and piperidine with acrylic acid and its derivatives.

(2) Alkali metal β-(aminothiocarbonylthio)propionates derived from cytisine and piperidine exhibit a pronounced insecticidal activity.

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