SYNTHESIS, ANTIFUNGAL, AND ANTIMICROBIAL PROPERTIES OF 1-THIOCYANATO-1-ALKOXYCARBONYL-2-ARYLETHANES

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It is known that aliphatic and aliphatic-aromatic thiocyanates are physiologically active compounds with a broad spectrum of biological activities; many of them have effective bactericidal properties [6, 8]. Of special interest as potential bactericides are 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes, which we have synthesized by using the anion-arylation reaction [3-5, 7].

It was found that aryldiazonium fluoroborates react vigorously with esters of acrylic and methacrylic acids in acetone or acetone–water (1:2) in the presence of potassium (sodium, ammonium) thiocyanate with loss of the nitrogen of the diazonium group and addition of the aryl and thiocyanate groups at the place of rupture of the multiple bond of the monounsaturated compound with formation of 1-thiocyanato-1-alkoxy-carbonyl-2-arylethanes:

$$R^1C_6H_4N_2BF_4 + CH_2{=}CR^2COOR^3 + MeSCN \rightarrow$$
$$\rightarrow R^1C_6H_4CH_2CR^2(SCN)COOR^3 + MeX + BF_3 + N_2$$

I–XXI

R^1=H(I, V, VI, X, XIV, XVIII), p-CH_3 (II, VII, XI, XV, XIX), m- CH_3 (III, VIII, XII, XVI, XX), p-CH_3O (IV, IX, XIII, XVII, XXI); R^2=H (I–V), CH_3(VI–XXI); R^3=CH_3 (I–IV, VI–IX), C_4H_9 (V, XIV–XVII), C_2H_5(X–XIII), iso-C_4H_9 (XVIII–XXI); Me=Na, K, NH_4.

The thiocyanatoarylation proceeds at temperatures from −30 to −15°C. The structure of the diazo salt of the monounsaturated compound and also the conditions at which the reaction is carried out (acetone or acetone–water) do practically not influence the yields of the 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes, which are 50-70%.

A necessary condition for satisfactory proceeding of the reaction is the presence of a catalyst, a copper(II) salt. Satisfactory catalysts for the thiocyanatoarylation reaction proved to be copper(II) acetate, basic carbonate, and tetrafluoroborate.

It was found that the reaction under investigation can also proceed without a catalyst, but in that case the yield of desired product is 40-50% lower than under catalytic conditions.

The structures of the 1-thiocyanato-1-alkoxycarbonyl-2-arylethanes were confirmed by IR and PMR spectroscopy. The IR spectra of compounds I-XXI contain intensive narrow absorption bands of the carbonyl and thiocyanato groups in the regions 1726-1740 and 2140-2150 cm^{-1}, respectively [1, 2]. The PMR spectra of the prepared compounds contain signals of the ester and methylene groups, and also of the protons of the aromatic nuclei. The PMR spectra of compounds I-V contain signals of the protons of the methylene and methyl groups. As a consequence of the chirality of the carbon atom, these protons give an ABX spin system and appear as multiplets in the regions 3.18-3.21 ppm and 3.89-3.93 ppm, respectively. In the PMR spectra of compounds VI-XXI signals of the methyl group are found.

EXPERIMENTAL (CHEMICAL)

IR spectra were recorded on a Specord 751R spectrometer. PMR spectra were taken from solutions in $CDCl_3$ on a Bruker CXP-90 spectrometer operating at 90 MHz. Chemical shifts were measured relative to the internal standard TMS. The purity of compounds I-XXI was checked by TLC on Silufol UV-254 plates with the eluent hexane–ether–chloroform 1:1:2. Found and calculated values of elemental analyses corresponded.

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TABLE 1. 1-Thiocyanato-1-alkoxycarbonyl-2-arylethanes

Compound	Yield, %	bp, °C/1 mm Hg	Empirical formula	Minimal inhibitory concentration, μ g/ml						
				E. coli	S. aureus	P. subt.	P. aerugin	S. cerevis	C. albicans	A. niger
I	72	133—135	$C_{11}H_{11}NO_2S$	500	31,2	7,8	250	125	62,5	500
II	64	142—144	$C_{12}H_{13}NO_2S$	>500	125	31,2	250	125	125	250
III	42	128—130	$C_{12}H_{13}NO_2S$	>500	500	7,8	250	125	125	250
IV	65	162—164	$C_{12}H_{13}NO_3S$	>500	125	62,5	500	250	500	500
V	59	155—157	$C_{14}H_{17}NO_2S$	>500	7,8	1,96	500	250	500	500
VI	71	132—134	$C_{12}H_{13}NO_2S$	>500	500	500	250	500	500	500
VII	60	135—137	$C_{13}H_{15}NO_2S$	>500	500	500	500	500	500	500
VIII	49	137—138	$C_{13}H_{15}NO_2S$	>500	500	500	500	500	500	500
IX	68	155—160	$C_{13}H_{15}NO_3S$	>500	500	500	250	500	500	500
X	45	125—127	$C_{13}H_{15}NO_2S$	>500	500	500	500	500	500	500
XI	63	139—140	$C_{14}H_{17}NO_2S$	>500	>500	500	250	500	500	500
XII	49	132—134	$C_{14}H_{17}NO_2S$	>500	500	500	500	500	500	500
XIII	64	135—140	$S_{14}H_{17}NO_3S$	>500	500	500	500	500	500	500
XIV	56	150—152	$C_{15}H_{19}NO_2S$	>500	500	500	250	500	500	500
XV	51	180—181	$C_{16}H_{21}NO_2S$	>500	500	500	250	500	500	500
XVI	41	158—160	$C_{16}H_{21}NO_2S$	>500	500	500	250	500	500	500
XVII	55	174—175	$C_{16}H_{21}NO_3S$	250	62,5	125	500	62,5	125	125
XVIII	74	139—139	$C_{15}H_{19}NO_2S$	>500	500	500	500	500	500	500
XIX	65	160—165	$C_{16}H_{21}NO_2S$	>500	500	500	500	>500	500	500
XX	43	158—164	$C_{16}H_{21}NO_2S$	>500	500	500	500	500	500	500
XXI	53	176—177	$C_{16}H_{21}NO_3S$	>500	500	500	500	>500	500	500

1-Thiocyanato-1-methoxy-2-phenylethane (I). To a mixture of 19.2 g (0.1 mole) of phenyldiazonium fluoroborate, 1 g (0.005 mole) of cupric acetate (II), 10.3 g (0.12 mole) of methyl acrylate, and 150 ml of acetone—water (1:2) was added over 10-15 min 19.4 g (0.2 mole) of potassium thiocyanate. Nitrogen was evolved at −30 to −15°C in 2 h. After the volution of nitrogen had stopped, the reaction mixture was extracted with 250 ml of ether, the extract was washed with water, and dried over magnesium sulfate. After evaporation and vacuum distillation we obtained 2.7 g (20%) of phenyl isothiocyanate, bp 69-71°C (1 mm Hg), d_4^{20} 1.1305, n_D^{20} 1.6494, and 15.9 g (72%) of compound I.

Compounds II-XXI were prepared in much the same way. Reactions with other copper salts and without them were carried out in the same way.

EXPERIMENTAL (BIOLOGICAL)

The antimicrobial activities of the prepared compounds were studied by the method of twofold serial dilution in liquid Sabouraud's medium with regard to the yeast fungi C. albicans and S. Cerevisiae, the filamentous fungus A. niger, and also by the method of twofold serial dilution in beef-extract broth with regard to Gram-positive (S. aureus), Gram-negative (E. coli, P. aeruginosa), and spore-forming (B. subtilus) bacteria.

As can be seen from Table 1, the compounds studied have weak antifungal activities with regard to the test strains used. Compounds I and XVII are distinguished for their antimycotic properties.

The study of the thiocyanates showed that they have weak antibacterial activity, with exception of compound V, which has distinct antistaphylococcal and antibacillar properties.

Of special interest are compounds I and IV, derivatives of which may have antibacterial properties.

The presence of a methyl or butyl radical in the ester group, and in the benzene ring, in addition to hydrogen, of a methoxy group at the para position, contributes to the development of antifungal and antibacterial activities.

LITERATURE CITED

1. D. Barton and I. Ollis, General Organic Chemistry [Russian translation], Vol. 5, Moscow (1983), p. 473.
2. L. Bellamy, New Data on IR Spectra of Complex Molecules [Russian translation], Moscow (1971), pp. 65, 69.
3. E. E. Bilaya, N. I. Ganushchak, N. D. Obushak et al., Zh. Obshch. Khim., 56, 1916-1917 (1986).
4. N. I. Ganushchak, B. D. Grishchuk, V. A. Baranov et al., Ukr. Khim. Zh., 43, No. 12, 1301-1303 (1977).

5. B. D. Grishchuk, P. M. Gorbovoi, and N. I. Ganushchak, Fifth All-Union Symposium on Organic Synthesis: Summaries [in Russian], Moscow (1988), p. 30.
6. N. N. Mel'nikov, Pesticides [in Russian], Moscow (1987), pp. 347-355.
7. N. D. Obushak, N. I. Ganushchak, E. E. Bilaya, and B. D. Grishchuk, 15th Ukrainian Republic Conference on Organic Chemistry: Summaries [in Russian], Uzhgorod (1986), p. 270.
8. S. Patai, The Chemistry of Cyanates and Their Thio Derivatives, Vol. 2, Jerusalem (1977).

SYNTHESIS AND FUNGICIDAL ACTIVITY OF SUBSTITUTED TETRAHYDRO-[3, 4-c]- AND BENZO[h]TETRAHYDROPYRIDO[3,4-c]COUMARINS

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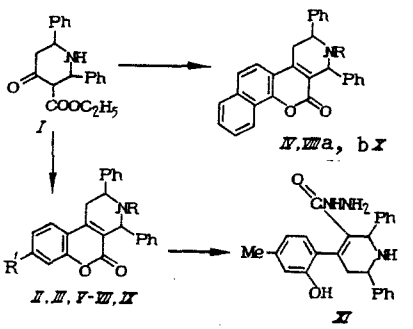
Pyridocoumarins have attracted the attention of investigators in connection with the possibility of using them as organic colors for lasers, luminophores, and fluorescent markers for biological objects [2, 3]. Information about the physiological activity of pyridocoumarins is limited.

With a view to study the fungicidal activity of compounds of this series, we have synthesized substituted 1,2,3,4-tetrahydropyrido[3,4-c]coumarins and 1,2,3,4-tetrahydrobenzo[h]-pyrido[3,4-c]coumarins; the starting compound was 2,6-diphenyl-3-ethoxycarbonylpiperidin-4-one (I). Earlier [4], from this β-ketoester and resorcinol 8-hydroxy-2,4-diphenyl-1,2,3,4-tetrahydropyrido[3,4-c] coumarin (II) was prepared with the Pechmann reaction, which synthesis we repeated in order to record its spectral characteristics and to prepare derivatives through the hydroxy and secondary ammonium groups.

By condensation under the same conditions of β-ketoester I with m-cresol and α-naphthol were prepared in quantitative yields 8-methyl-2,4-diphenyl-1,2,3,4-tetrahydropyrido[3,4-c] coumarin (III) and 2,4-diphenyl-1,2,3,4-tetrahydrobenzo[h]pyrido[3,4-c]-coumarin (IV), respectively. Data on these compounds are listed in Table 1. In the IR spectra of compounds II-IV are found an intensive band of the lactone carbonyl and absorption bands of the C=C and NH bonds of the piperidine fragment, and their UV spectra have absorption maxima of the coumarin system in the region 284-367 nm. PMR spectral data also confirm the structures of compounds II-IV (Table 2).



R=H(II—IV,VI), Ac(V,VII,VIIIa), EtCO(VIIIb), Me(IX,X);
R'=OH(II), Me(III,VII,IX), AcO(V,VI)

By reacting compound II with Ac_2O in dry pyridine was prepared 2,4-diphenyl-3-acetyl-8-acetoxy-1,2,3,4-tetrahydropyrido[3,4-c]coumarin (V), which on heating in aqueous pyridine

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