SYNTHESIS OF BIOLOGICALLY ACTIVE HYDRAZONES AND SUBSTITUTED PYRAZOLES FROM β,β-DICHLOROVINYL KETONES

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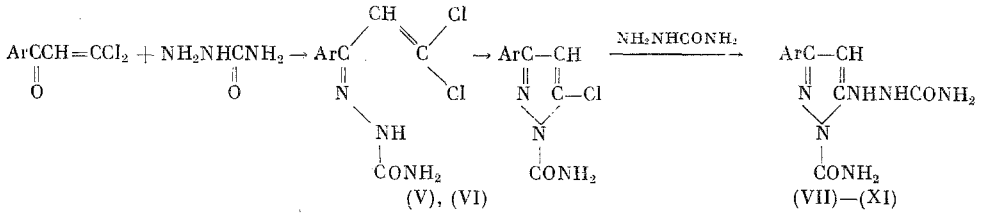
Hydrazones have broad biological activity, and antituberculosis, antivariola, antileukemic, and other drugs have been synthesized on their basis [1]. We have previously [2, 3] shown that β,β-dichlorovinyl ketone 2,4-dinitrophenylhydrazones are active against influenza virus A2G1/68 in experiments on chick embryos. Substances with antiviral and antibacterial activity have also been found among the β,β-dichlorovinyllactams [5] and β,β-dichlorovinyl amides of aromatic carboxylic acids [6]. It is known [5] that β,β-dichlorovinylpyrrolidone has a stimulatory psychotropic effect, similar to the effect of caffeine and Phenamine. We have continued the search for biologically active substances among compounds containing the β,β-dichlorovinyl group.

In the present work we studied the reaction of β,β-dichlorovinyl alkyl(aryl) ketones [7] and β,β-dichloroacrolein with semicarbazide, thiosemicarbazide, and hydrazine. Since the ketones cited contain two electrophilic centers, the traditional reaction path involving the C=O group is complicated in some cases by the involvement of the C−Cl bonds.

Alkyl β,β-dichlorovinyl ketones react with acetic acid semicarbazide in an alcoholic medium to form the corresponding semicarbazones (I-IV) (Table 1). Depending on the conditions, the aromatic ketones produce semicarbazones V and VI or carbaminopyrazoles VII-XI (see Table 1).



Semicarbazones V and VI were obtained when phenyl and p-chlorophenyl β,β-dichlorovinyl ketone were heated for 10-30 min to 60°C with acetic acid semicarbazide in ethanol, while prolonged boiling (2 h) with an excess of semicarbazide results in the synthesis of the carbaminopyrazoles. The observed difference may be attributed to the greater mobility of the chlorine atoms in aromatic ketones and the syn configuration of the initially formed semicarbazones in analogy to the 2,4-dinitrophenylhydrazones of aromatic ketones [3], which promote their cyclization.

Unlike V and VI, the compounds of the aliphatic series (I-IV) decompose when heated above the melting point with the release of HCl, but pyrazoles do not form.

The structure of compounds I-XI is confirmed by their spectral characteristics. The IR spectra of I-VI contain a group of bands which are characteristic of semicarbazones (Table 2) [8, 9]. The presence in the PMR spectrum of semicarbazone II of singlet signals of protons in the CH_3 and CH groups (in CD_3CD, δ 2.07 and 6.39 ppm; in $CDCl_3$, δ 2.02 and 6.46 ppm, respectively) attests to the existence in the form of one isomer. In the IR spectrum of carbaminopyrazoles VII-XI the vibrations of the benzene and pyrazole rings overlap and are characterized by a group of unresolved bands in the 1580-1600- and 3050-3060-cm^{-1} regions (see Table 2). In the PMR spectrum of carbaminopyrazole VII the signal of the olefinic proton (δ 6.04 ppm) is shifted to a stronger field in comparison to the analogous signal in the spectrum of semicarbazone V (7.08 ppm). The

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TABLE 1. Melting Points and Data from the Elemental Analysis of Semicarbazones I-VII, Carbaminopyrazoles VII-XI, Thiosemicarbazones XII-XV, and Pyrazole XVI

Compound	R	Yield, %	mp, °C (ethanol)*	Found, %					Empirical formula	Calculated, %				
				C	H	Cl	N	S		C	H	Cl	N	S
(I)	H	92	136	–	–	39,05	23,29		$C_4H_5Cl_2N_3O$	–	–	38,95	23,07	
(II)	CH_3	87	160	30,78	3,70	36,21	–		$C_5H_7Cl_2N_3O$	30,64	3,60	36,17	–	
(III)	C_2H_5	86	169	–	–	33,68	–		$C_6H_9Cl_2N_3O$	–	–	33,75	–	
(IV)	C_3H_7	87	146	–	–	30,90	–		$C_7H_{11}Cl_2N_3O$	–	–	31,62	–	
(V)	C_6H_5	86	166	46,11	3,51	27,18	–		$C_{10}H_9Cl_2N_3O$	46,53	3,51	27,12	–	
(VI)	p-ClC_6H_4	68	173–174	–	–	36,10	–		$C_{10}H_8Cl_2N_3O$	–	–	36,02	–	
(VII)	C_6H_5	74	234–236	49,65	4,62	–	32,46		$C_{11}H_{12}N_6O_2$	50,76	4,64	–	32,29	
(VIII)	p-$NO_2C_6H_4$	70	22	43,42	3,47	–	32,60		$C_{11}H_{11}N_7O_8$	43,29	3,63	–	32,13	
(IX)	m-$NO_2C_6H_4$	78	219	43,14	3,76	–	31,21		$C_{11}H_{11}N_7O_8$	43,29	3,63	–	32,13	
(X)	$CH_3C_6H_4$	80	207	–	–	–	29,80		$C_{12}H_{14}N_6O_2$	–	–	–	30,64	
(XI)	$CH_3OC_6H_4$	72	204	52,20	4,86	–	27,11		$C_{22}H_{14}N_6O_3$	49,64	4,86	–	28,94	
(XII)	H	80	96	–	–	34,41	–	15,64	$C_4H_5Cl_2N_3S$	–	–	35,80	–	16,19
(XIII)	CH_3	66	86	–	–	32,24	–	15,62	$C_5H_7Cl_2N_3S$	–	–	33,42	–	15,12
(XIV)	C_2H_5	65	100	–	–	31,52	–	13,80	$C_6H_9Cl_2N_3S$	–	–	31,36	–	14,17
(XV)	C_3H_7	60	100	–	–	29,40	–	13,32	$C_7H_{11}Cl_2N_3S$	–	–	29,52	–	13,33
(XVI)	CH_3	40,6	171–176	35,51	5,19	39,31	20,08	–	$C_8H_{11}Cl_3N_4$	35,64	4,11	39,45	20,78	–

* The carbaminopyrazoles and thiosemicarbazones melt with decomposition, and the semicarbazones decompose above the melting point.

TABLE 2. Characteristic Frequencies (cm^{-1}) in the IR Spectra of β,β-Dichlorovinyl Semicarbazones* and Carbaminopyrazoles VII and IX

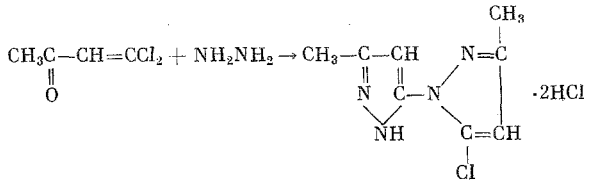
Compound	R	Free NH	Associated NH	CH= (CH=CCl$_2$)	C=O		C=N	C=C	CCl
					amide I	amide II			
(I)	H	3460	3350, 3280 3225, 3160	3080	1730	1660	1602	1565	860
(II)	CH_3	3470	3365, 3280 3230, 3170	3060	1735	1695	1625	1585	850, 860
(III)	C_2H_5	3450	3355, 3280 3230, 3200	3040	1692 sh	–	1632	1580	840, 850
(IV)	C_3H_7	3465	3350, 3290 3200	3040	1680 sh	–	1620	1570	840, 850
(V)	C_6H_5	3480	3355, 3330 3260, 3190	–	1690	1675	1590	1570	840
(VI)	p-ClC_6H_4	3490	3355, 3300 3200		1692	1660	1590	1580	
(VII)	C_6H_5	3460	3413, 3330 3215		1725	1660	1600	1570	
(IX)	m-$NO_2C_6H_4$	3460	3335, 3290		1720	1680	1590	1570	

* The frequencies in the spectra were assigned on the basis of the data in [8, 9] and the IR spectra of the original ketones [10].

positions of the signals of the phenyl protons in the PMR spectra of compounds V and VII are identical (7.59 ppm), and the signals of the =CH and NH_2 protons for compounds V, VII, and VIII are superimposed and found, respectively, at 7.08, 6.04, and 6.24 ppm. Separation of these signals is observed upon heating to 60°: in VII, 6.04 (=CH) and 5.94 ppm (NH_2); in VIII, 5.24 (=CH) and 6.08 ppm (NH_2).

Thiosemicarbazones XII-XV (see Table 1) were obtained by reacting alkyl β,β-dichlorovinyl ketones with thiosemicarbazide in a neutral water–alcohol medium at 20°C. The aromatic ketones, as in the case of the reaction with semicarbazide, react in a complex manner with the participation of the C=O group and the C–Cl bonds. The unreacted ketone was always recovered and a mixture of unidentified products containing sulfur, nitrogen, and chloride according to the data from the elemental analysis and decomposing upon storage with the evolution of a gas always formed with various ratios between the aromatic ketone and the thiosemicarbazide, temperatures, times, and pH values. The formation of a precipitate of AgCl when the water–alcohol solutions of these products were mixed with an $AgNO_3$ solution and the presence in the IR spectra of absorption bands at 2500-2800 cm^{-1} point out the presence of an $>\overset{+}{N}H\cdot Cl^-$ group. In the IR spectra of these products there are no absorption bands of the C=O, C=C, and C–Cl groups of the original ketones [10].

β,β-Dichlorovinyl ketones react with 2,4-dinitrophenyl- and phenylhydrazine to form ordinary hydrazones [2]. In contrast, the more basic compound hydrazine reacts with methyl β,β-dichlorovinyl ketone, yielding 3-methyl-5-(3'-methyl-5'-chloropyrazolyl)pyrazole hydrochloride (XVI):



(XVI)

The structure of XVI was confirmed by the PMR spectrum, which contains the protons signals at 2.15 and 2.29 ppm (CH_3) and at 5.84 and 6.68 ppm (CH) of equal intensity (in $CDCl_3$ and DMSO). The IR spectrum contains absorption bands of the C=N bond at 1630 cm^{-1} and $>\overset{+}{N}H$ at 2600-2800 cm^{-1}. The investigations of the antiviral (influenza virus A2G1/68) and antistaphylococcal activity (Staphylococcus aureus, strain 209-R and the set of antibiotic-resistant strains Nos. 3132, 3197, and 3234, model of an influenza–staphylococcal infection of chick embryos) showed that among the compounds obtained there are substances which have pronounced biological activity.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 instrument in the 600-3600-cm^{-1} region in tablets with KBr, and the PMR spectra were recorded on a Tesla BS487-C spectrometer at 80 MHz in ~10% solutions in DMSO.

Methyl β,β-Dichlorovinyl Ketone Semicarbazone (II). A ground mixture of semicarbazide hydrochloride and 8 g of anhydrous AcONa was boiled in 120 ml of ethanol in a water bath for 2 h, after which the mixture was filtered. The filtrate was added to an ethanol solution of 8.3 g (0.06 mole) of methyl β,β-dichlorovinyl ketone, and the mixture was heated for 30 min at 60°C and given an addition of water to persistent turbidity. After 2 h, the precipitate was filtered and washed with water and cold ethanol. This yielded 11 g (87%) of II, mp 160°C (ethanol). Compounds I, III, and IV were obtained in an analogous manner (see Table 1).

Heating (60°C) 2 g of β,β-dichlorovinyl phenyl ketone with acetic acid semicarbazide (from 2.1 g of semicarbazide hydrochloride and 1 g of AcONa) in 10 ml of ethanol for 15 min yielded 1.6 g (70%) of V. Compound VI was obtained in a similar manner.

1-Carbamino-3-phenyl-5-semicarbazidopyrazole (VII). A ground mixture of 20.4 g of semicarbazide hydrochloride and 16.4 g of anhydrous AcONa was boiled for 2 h in 250 ml of ethanol and filtered. The filtrate was added to a solution of 20 g (0.1 mole) of phenyl β,β-dichlorovinyl ketone in 50 ml of ethanol and boiled for 3 h, and the precipitate was filtered. This yielded 19.2 g (74%) of VII.

Compounds VIII-XI were obtained in a similar manner (see Table 1).

Methyl β,β-Dichlorovinyl Ketone Thiosemicarbazone (XIII). An ethanolic solution of 4.6 g (0.05 mole) of thiosemicarbazide was added to a solution of 7 g (0.05 mole) of methyl β,β-dichlorovinyl ketone in ethanol, the mixture was heated for 30 min at 60°C, and diluted with water, and the precipitate was filtered and dried.

This yielded 7 g (71%) of thiosemicarbazone XIII, which decomposes upon heating.

Compounds XII, XIV, and XV were obtained in a similar manner.

3-Methyl-5-(3'-methyl-5'-chloropyrazolyl)pyrazole Hydrochloride (XVI). A solution of 13.9 g (0.1 mole) of methyl β,β-dichlorovinyl ketone in 100 ml of ethanol was slowly added to a solution (0.02 mole) of 13.7 g of hydrazine hydrochloride in a minimal quantity of water. The mixture was heated for 1 h at 60-50°C and held for 10 h at 20°C. The solvents were distilled off, and the precipitate was washed on the filter with cold water (0°C) and dried. This yielded 7 g of pyrazole XVI, mp 171-176°C (ethanol).

CONCLUSIONS

1. Alkyl β,β-dichlorovinyl ketones react with semicarbazide and thiosemicarbazide to form hydrazones, while aryl β,β-dichlorovinyl ketones react with semicarbazide to form previously unknown N-carbaminopyrazoles.

2. The reaction of methyl β,β-dichlorovinyl ketone with hydrazine yields 3-methyl-5-(3'-methyl-5'-chloropyrazolyl)pyrazole.

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