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REACTION OF α-ALKOXYACROLEINS WITH SEMICARBAZIDE AND ITS S-, Se-, AND NH-ANALOGS

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Thiosemicarbazones [1] and guanyl hydrazones [2] of several aliphatic aldehydes have a wide spectrum of physiological activities. With the objective of synthesis of new biologically active compounds we studied the reaction of α-alkoxy(phenoxy)acroleins with hydrazine derivatives having the general formula $NH_2NHCXNH_2$ where X = O, S, Se, NH. For comparative estimation of the nucleophilic properties of the amino groups of these compounds it was necessary to determine their basicity constants $(pK_aBH)^+$ which in aqueous solution are known only for three of the compounds studied (Table 1). Potentiometric titration of the selenium analog in an aqueous solution showed that under these conditions the selenosemicarbazide does not have basic properties. Determination of the basicity of all the hydrazine derivatives in a CH_3CN medium (see Table 1) showed that the relative basicities of the known members of the series are in the same order as they are in the aqueous solution. From the table it is evident that because of the very low basicity of the selenium analog a very low yield of its derivative should be expected.

Carrying out the reaction of α-alkoxy(phenoxy)acroleins with semi-, thiosemi- and selenosemicarbazides in a weakly basic medium (pH 8-9) makes it possible to obtain semicarbazones (Ia-f), and in so doing to successfully avoid hydrolysis of the vinyloxy group of the carbonyl compound

$$CH_2{=}C(OR)CHO + NH_2NHCXNH_2 \rightarrow CH_2 = C(OR)CH{=}NNHCXNH_2 \quad \text{(I a-f)}$$

R = C_2H_5, X = O (a); R = C_2H_5, X = Se (b); R = C_2H_5, X = S (c); R = CH_3, X = S (d); R = C_4H_9, X = S (e); R = C_6H_5, X = S (f)

Yields and constants for (Ia-f) are shown in Table 2. For the compounds with X = S, Se a correspondence between their basicity and the yield of reaction products was noted. Lowering of the yield in the case where X = O was caused by the side reaction of decomposition of the starting hydrazine in the basic medium. On carrying out the reaction with guanyl hydrazine in a basic medium the formation of guanyl hydrazones of α-alkoxyacroleins was not observed. This was due to the fact that at pH 8-9 the hydrochloride of aminoguanidine [5] is 99% in the form of the resonance stabilized cation $NH_2 \rightarrow NH\underset{^{+}NH_2}{C}-NH_2$. The presence of a positive charge in this structure brings about a pronounced weakening of the electron-donor capability of the

TABLE 1. Basicity Constants of $NH_2NHCXNH_2$ in Water and CH_3CN at 20°C

X	pK_aBH^+	
	H_2O	CH_3CN
Se		7,71
S	1,88 [3]	8,34
O	3,86 [4]	11,89
NH	11,04 [3]	21,50

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TABLE 2. Constants for (Ia-f), (IIa, b), and (IIIa)

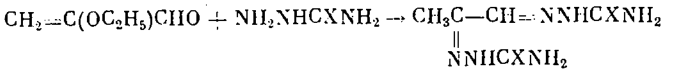
Compound	R	X	Yield, %	Mp., °C	Calculate %				Formula	Found, %			
					C	H	N	S(Se)		C	H	N	S(Se)
(Ia)	C_2H_5	O	64	182	46,22	6,82	26,86		$C_6H_{11}N_3O_2$	46,00	7,05	26,80	
(Ib)	C_2H_5	Se	60	160	32,40	4,87		35,10	$C_6H_{11}N_3OSe$	32,70	5,00		35,90
(Ic)	C_2H_5	S	80	152	41,37	6,45	24,33	18,50	$C_6H_{11}N_3OS$	41,60	6,40	24,20	18.20
(Id)	CH_3	S	76	161	37,95	5,90	26,25	20,62	$C_5H_9N_3OS$	37,90	5,65	26,00	20,01
(Ie)	C_4H_9	S	77	165	44,04	6,52	20,02	15,00	$C_8H_{15}N_3OS$	44,44	6,48	19,44	14,95
(If)	C_6H_5	S	74	175	54.46	4,92	19,12	14,14	$C_{10}H_{11}N_3OS$	54,30	4,97	19,00	14,50
(IIa)		O	90	250	32,26	5,37	45,16		$C_5H_{10}N_6O_2$	31,94	5,36	44,95	
(IIb)		Se	58	238	19,31	3,27		50,65	$C_5H_{10}N_6OSe_2$	19,23	3,20		50,64
(IIIc)		O	60	205	37,02	5,41	32,80		$C_4H_7N_3O_2$	37,10	5,41	33,40	

TABLE 3. PMR Spectral Parameters (in DMSO) of (Ia-c), (IIa, b), and (IIIa)

Compound	R	X	δ, ppm							J, Hz (=CH₂)
			=CH₂	CH=N	NH	NH₂	OCH₂	CH₃ ethyl	CH₃	
(Ia)	C_2H_5	O	4,37 d 4,46 d	7,23 s	10,08	6,13	3,78 s	1,22 t		2,5
(Ib)	C_2H_5	Se	4,70 d 4,60 d	7,57 s	11,64	8,66 8,00	3,80 s	1,22 t		2,5
(Ic)	C_2H_5	S	4,50 d 4,64 d	7,45 s	11,34	8,10 7,33	3,77 s	1,22 t		2,5
(IIa)		O		7,62 s	10,50	6,60			2,12	
(IIb)		Se		8,02 s	10,87 12,24	8,72 9,10			1,95	
(IIIa)		O		7,37 s	11,87	6,97			2,12	

reacting NH_2 group. For this reason the aminoguanidine hydrochloride does not participate in the reaction in a basic medium.

The reaction of α-ethoxyacrolein with excess semi-and selenosemicarbazides in an acidic medium leads to the formation of disemicarbazones of methyl glyoxal (IIa, b)



$$CH_2{=}C(OC_2H_5)CHO + NH_2NHCXNH_2 \rightarrow \underset{\underset{NNHCXNH_2}{\|}}{CH_3C}{-}CH{=}NNHCXNH_2 \quad \text{(IIa, b)}$$

$X = O$ (a); $X = Se$ (b)

A study of the hydrolysis of compound (I) in the case of the semi- and selenosemicarbazones of α-ethoxyacrolein in an acid medium showed that (Ia) is converted into the monosemicarbazone of methyl glyoxal (IIIa)

$$\underset{\text{(Ia)}}{CH_2{=}C(OC_2H_5)CH{=}NNHCONH_2} + H_2O \xrightarrow{H^+} \underset{\text{(IIIa)}}{CH_3COCH{=}NNHCONH_2}$$

The hydrolysis of the selenosemicarbazone of α-ethoxyacrolein (Ib) at pH 3 results in the splitting of the selenosemicarbazone fragment, (see [6]) but under milder conditions (AcOH, pH 4-6) the starting compound is recovered.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument, PMR spectra on a Tesla BS-487 (80 MHz) instrument with HMDS or TMS as internal standards, UV spectra on a Specord UV-VIS instrument. d-Alkoxyacroleins were obtained as in [7].

General Method of Obtaining Semi-, Selenosemi-, and Thiosemicarbazones of α-Alkoxyacroleins (Ia-f). To a solution of 0.1 mole of semicarbazide $NH_2NHCXNH_2$ where X = O, Se, S (the semicarbazide is used in the form of the hydrochloride) in a 35:15 water—methanol mixture was added NaOH to a pH of 8-9 and 0.1 moles of α-alkoxy(phenoxy)acrolein. The mixture was heated 5 min at 50°C. On cooling a precipitate was formed which was filtered, washed with ether, and dried. The yields, melting points, and elemental analysis data are shown in Table 2, the PMR spectra in Table 3.

IR spectra for (Ia-e) (ν, cm^{-1}; KBr) 3100-3450 (NH and NH_2), 1612 (C=C), 1540 and 1580 (NH_2 and C=N), 1100 (C=S), 830 (=CH_2).

Disemicarbazone of Methylglyoxal (IIa). To a solution of 11.25 g (0.1 moles) of semicarbazide hydrochloride in a 35:15 water—methanol solution was added 5 g (0.05 moles) α-ethoxyacrolein, heated at 50°C for 1 h, the precipitate (IIa) filtered, washed with ether, and dried. For the yield and constants see Tables 2, 3.

Diselenosemicarbazone of Methylglyoxal (IIb). To 0.56 g (0.0056 moles) of α-ethoxyacrolein was added 1 g (0.55 moles) of water, conc. HCl to a pH of 4, then stirred at 40°C for 2 h, a solution of 1.5 g (0.0112 moles) of selenosemicarbazide in a 35:15 water—ethanol mixture was added and heated at 40°C for 5 min. There was obtained 1 g (58%) of a yellow precipitate of (IIb).

Hydrolysis of (Ia). A solution of 15.7 g (0.1 moles) of (Ia) in a 1:1 water—methanol mixture was acidified with HCl to pH 3 and stirred 0.5 h at 60°C. The precipitate which came out on cooling was filtered, washed with ether and dried. The compound obtained was (IIIa) (see Tables 2, 3). IR spectrum (ν, cm^{-1}, KBr): 1100, 1540, 1580, 1682, 1700, 3010, 3180, 3250, 3350.

Determination of the Basicity Constant. The value of pK_aBH^+ of the conjugate acids of the bases being investigated was determined by the method of potentiometric titration [8]. The pK_aBH^+ of thiosemi- and selenosemicarbazides were determined in anhydrous MeCN, using the titrant 0.1 N $HClO_4$ in MeCN, and a standard base diphenyl guanidine with a pK_a 17.9 [9]. Semicarbazide and aminoguanidine in the form of hydrochlorides have limited solubilities, hence in determining their basicities a mixture of MeCN—MeOH is employed in a ratio of 4:1. A 0.1 N solution of Bu_4NOH in a 9:1 mixture of $C_6H_6-CH_3OH$ serves as the titrant. Benzoic acid was used as the standard, the pK_a of which is 20.7 in MeCN [10].

CONCLUSIONS

1. The reaction of α-alkoxyacroleins with semi-, thiosemi-, and selenosemicarbazides in a basic medium leads to the formation of semi- , thiosemi- , and selenosemicarbazones of α-alkoxyacrolein. The reactions of α-ethoxyacroleins with twofold excess amounts of semi- and selenosemicarbazides in acid media lead to disemi- and diselenosemicarbazones of methylglyoxal.

2. Determination of basicity constants of semicarbazide and its S-, Se-, and NH-analogs was carried out in acetonitrile.

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