SYNTHESIS AND BIOLOGICAL ACTIVITY OF ORGANYLTHIOSELENIDES

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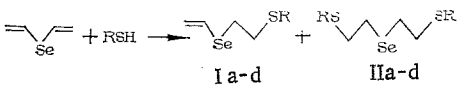
UDC 615.281:547.379.1]0.12.1

The biochemistry of selenium, which for many years was considered to be a toxic element, and even a possible cancerogen, is at present being developed. The possible biological role of this element, first shown in [1], was the reason for studying the properties of organoselenium compounds, from which compounds with anticancerous [2], antihistaminic [3], and bactericidal activity [4] were obtained. It was found [5] that a deficiency of selenium in the organism may cause a susceptibility to cardiovascular and cancerous diseases, provoke arthritis, cataract, and caries of the teeth. Selenium is included in the composition of active groups of certain enzymes and proteins, which are antioxidants and antidotes for several cancerogens [5].

There, broadening of the scope of investigations on the synthesis and study of organoselenium compounds in a search for new physiologically active compounds is an urgent problem. The present work describes the synthesis and study of biological properties of 2-(organylthio)-ethyl vinyl selenides (I) and 2,2'-di(organylthio)diethyl selenides (II), on which there is very limited information in the literature. Only one representative of these selenides has been described, 2,2'-di(phenylthio)diethyl selenide, obtained from the difficultly available and extraordinarily toxic di-(2-bromoethyl) selenide, an analog of yperite (mustard gas), and thiophenol [6]. It should be noted that this method is inapplicable to the synthesis of vinyl selenides I.

To develop a suitable and universal method for the preparation of organylthioselenides I and II, we were the first to carry out and study the reaction of divinyl selenide with thiols and found that it proceeds readily on heating (60-85°C) the reagents in the presence of azobisisobutyronitrile.



Ia-d IIa-d

Ia, IIa: R = C_2H_5; Ib, IIb: R = C_3H_7; Ic R = iso-C_3H_7; IIc: R = iso-C_4H_9; Id, IId: R = C_6H_5.

To obtain monoadducts I, a three- to fivefold excess of divinyl selenide with respect to the thiol should be used. The diadducts were synthesized in the presence of a twofold (compared with the stoichiometric amount) excess of the thiol with respect to divinyl selenide. The yield of selenides I and II is 31-64% (Table 1). The initial divinyl selenide is at present available because of the effective method for its preparation from acetylene and elementary selenium [7].

The physicochemical characteristics and data of the elemental analysis of compounds I and II are listed in Table 1, and the characteristics of their PMR spectra in Table 2.

EXPERIMENTAL CHEMISTRY

The PMR spectra were run on the spectrometer from the firm Tesla BC 487C (CSSR) in CCl_4, using hexamethyldisilane as internal standard.

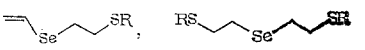
The Irkutsk Institute of Organic Chemistry, Siberian Branch of Academy of Sciences of the USSR. The Irkutsk Medicinal Institute, Siberian Branch of All-Union Scientific Surgery Center, Academy of Medical Sciences of the USSR, Irkutsk. Translated from Khimiko-farmatsevticheskii Zhurnal, Vol. 18, No. 1, pp. 26-28, January, 1984. Original article submitted June 27, 1983.

0091-150X/84/1801-0011$08.50

TABLE 1. 2-(Organylthio)ethyl Vinyl Selenides (Ia-d) and 2,2'-Di(organylthio)diethyl Selenides (IIa-d)

Compound	Yield, %	b_p, °C (mm Hg) mp, °C	d_4^{20}	n_D^{20}	Found, % C	Found, % H	Empirical formula	Calculated, % C	Calculated, % H
Ia	64	64 (1)	1,2880	1,5542	36,88	6,10	$C_6H_{12}SSe$	36,92	6,20
Ib	60	72 (1)	1,2517	1,5473	40,57	6,62	$C_7H_{14}SSe$	40,19	6,74
Ic	54	68 (1)	1,2436	1,5452	40,37	6,67	$C_7H_{14}SSe$	40,19	6,74
Id	31	118 (1)	1,4366	1,6273	42,29	4,73	$C_{10}H_{12}SSe$	49,38	4,97
IIa	60	125 (1); 21	—	—	37,63	6,68	$C_8H_{18}S_2Se$	37,34	7,05
IIb	58	140 (1); 31	—	—	42,50	7,46	$C_{10}H_{22}S_2Se$	42,09	7,77
IIc	55	145 (1); 37	—	—	46,08	8,31	$C_{12}H_{26}S_2Se$	45,99	8,36
IId	40	58 (ether)	—	—	54,37	5,33	$C_{16}H_{18}S_2Se$	54,38	5,13

TABLE 2. Data of PMR Spectra of Selenides I and II



Compound	R* C_α	R* C_β	R* C_γ	R* =CH	Chemical shifts, δ, ppm (J, Hz) =CH_2 trans	=CH_2 cis	SCH_2CH_2Se	radical protons H_α	H_β	H_γ
Ia	CH_2	CH_3	—	6,62 q	5,66 d (9,9)	5,39 d (16,9)	2,80 m	2,55 q	1,24 t	—
Ib	CH_2	CH_2	CH_3	6,61 q	5,66 d (10,0)	5,38 d (16,9)	2,78 m	2,49 t	1,60 m	0,99 t
Ic	CH	$(CH_3)_2$	—	6,62 q	5,67 d (9,9)	5,38 d (17,0)	2,79 m	2,88 q	1,25 d	—
Id	C_6H_5	—	—	6,62 q	5,67 d (10,0)	5,39 d (17,0)	2,93 m	7,17	—	—
IIa	CH_2	CH_2	—	—	—	—	2,70 m	2,53 q	1,24 t	—
IIb	CH_2	CH	CH_3	—	—	—	2,70 m	2,48 t	1,61 m	0,99 t
IIc	CH_2	—	$(CH_3)_2$	—	—	—	2,75 m	2,42 d	1,77 m	1,02 d
IId	C_6H_5	—	—	—	—	—	2,69 m‡ 3,03 m†	7,30 m	—	—

*The carbon atoms in the radical are indicated in order of their distance from the heteroatom.
†Protons of SCH_2 fragment.
‡Protons of $SeCH_2$ fragment.

2-(Ethylthio)ethyl Vinyl Selenide (Ia). A mixture of 4 g (0.03 mole) of divinyl selenide, 0.37 g (0.006 mole) of ethanethiol, and 0.044 g of azobisisobutyronitrile is charged into an ampul that has been purged with argon. The ampul is sealed and heated at 60-65°C for 6 h, and then the contents are distilled *in vacuo* to yield 0.7 g (64%) of Ia.

Compounds Ib-d were synthesized in a similar way.

2,2'-Di(ethylthio)diethylselenide (IIa). A mixture of 1.98 g (0.015 mole) of divinyl selenide, 3.65 g (0.06 mole) of ethanethiol and 0.056 g of azobisisobutyronitrile is charged into an ampul that has been purged with argon. The ampul is sealed and heated for 92 h at 80-85°C. The contents are distilled *in vacuo* to yield 2.3 g (60%) of IIa.

Compounds IIb, c were synthesized in a similar way.

2,2'-Di(phenylthio)diethyl Selenide (IId). A mixture of 0.95 g (0.0071 mole) of divinyl selenide, 3.14 g (0.0285 mole) of thiophenol, and 0.04 g of azobisbutyronitrile is charged in an ampul that has been purged with argon. The ampul is sealed and heated for 80 h at 80-85°C. The excess of thiophenol is distilled *in vacuo*, and the residue is recrystallized in cold (from −70 to −50°C) from ether to yield 0.72 g (40%) of IId.

EXPERIMENTAL PHARMACOLOGY

The acute toxicity and antitumorigenic activity were studied on nonpedegree white mice of two sexes, weighing 20-24 g each. The acute toxicity parameters were determined by the Kerber method with intraperitoneal administration. The values of mean lethal doses (LD_{50}) vary within 12 mg/kg (IId) to >200 mg/kg (Ia-d, IIb-c) and show that the compounds studied are little and moderately toxic materials [8]. In general, the monoadducts I are more toxic than the di(organylthio) selenides II.

The cytotoxic effect was tested on grafted Ehrlich and Fischer tumors, sarcoma 37, and NK/Ly. To the mice of the experimental and control groups, $5 \cdot 10^6$ tumor cells were introduced intraperitioneally. After 48 h, one of the preparations tested (in the form of oily solutions) was administrered intraperitoneally to the experimental animals, and the once daily administration was continued for the next 5 days [9, 10]. Eight days from the beginning of the experiment, all the animals were killed, and the per weight amounts of the tumors that

they have developed were determined. In the series studied, 2,2'-di(phenylthio)diethyl selenide (IId) had distinctly expressed cytotoxic properties with a selective effect: It inhibited the development of Ehrlich's ascites carcinoma in the experimental animals by 44%, compared with that for the control group animals. The remaining compounds were less active.

The antibacterial properties of selenides I and II were studied by the method of serial dilutions [10] and by the wells method [11]. In the first case, a series of dilutions of the compounds studied were prepared on a liquid culture medium, followed by inoculation of a minimal bacteriostatic concentration into the corresponding culture medium for counting the viable cells.

In the second method, wells were made in the agar medium, the culture medium was inoculated with "grass," and 0.2 ml of the compound studied diluted to a given extent were introduced into the wells. The antimicrobial activity was determined from the growth inhibition zone of the culture around the well. The tests were carried out with a spectrum of 10 strains of microorganisms (gram-positive bacteria: *Staphylococcus albus*, *Staphylococcus aureus*, *Staphylococcus cytricus*, *Bacillus anthracis*, hay bacillus, sarcine; gram-negative bacteria: *Escherichia coli*, *Proteus vulgaris*, *Bacillus pyocyaneous*, and *Salmonella typhimurium*. Compounds IIa and IId inhibited the growth of *Staphylococcus albus* and sarcine in a dose of 50 μg/ml. The remaining organylthio selenides did not inhibit or suppress the growth of these microorganisms at a concentration of 200 μg/ml.

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