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SYNTHESIS OF COMPLEX COMPOUNDS OF METHYL DERIVATIVES OF 8-QUINOLINESELENOL WITH METALS AND THEIR CYTOTOXIC ACTIVITY

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A series of 2-methyl-, 4-methyl-, and 2,4-dimethyl-8-quinolineselenolates of zinc, cadmium, mercury, nickel, palladium, platinum, arsenic, antimony, and bismuth has been synthesized and their cytotoxicity has been studied on HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), B16 (mouse melanoma), and Neuro 2A (mouse neuroblastoma) tumor cells. Mercury complexes were distinguished by high cytotoxicity on all the cell lines. Palladium complexes possessed somewhat lower activity and were significantly less toxic in relation to normal NIH 3T3 mouse embryo fibroblasts. All the studied metal 2-methyl-8-quinolineselenolates displayed high cytotoxicity on B16 melanoma, arsenic 4-methyl-8-quinolineselenolate acted most effectively on HT-1080 and MG-22A cells. Di(4-methyl-8-quinolyl) diselenide also possessed high cytotoxicity on these same cells.

Keywords: metal methyl-8-quinolineselenolates, cytotoxicity.

Organic and inorganic derivatives of selenium effectively inhibit the growth of a series of tumors [1-19]. One of the mechanisms proposed for explaining this action is based on the cytotoxic action of selenium on tumor cells [17-19].

The first organoselenium compound inhibiting the development of various tumors was *p*-methoxybenzeneselenol (**1**) [20-22]. Dibenzyl diselenide (**2**) displayed chemopreventive properties on a model tumor of rat large intestine caused by azoxymethane [23, 24]. We showed that 8-methylselenoquinoline (**3**) possesses a weak cytotoxic action. Di(8-quinolyl) diselenide (**4**) is significantly more active in relation to human HT-1080 fibrosarcoma cells. Metal 8-quinolineselenolates **5** possess high cytotoxicity, especially the complexes of mercury, cadmium, and gallium, and also arsenic derivatives [25].

To clarify the influence of the nature of the ligand and metal on the cytotoxicity of organoselenium compounds we have synthesized a series of complexes **6** of 2-methyl-, 4-methyl-, and 2,4-dimethyl-8-quinolineselenol with metals by the interaction of the appropriate selenol with metal salts. Their cytotoxicity has been studied on 4 lines of tumor cells (Tables 1-3), *viz*. HT-1080 human fibrosarcoma, MG-22A mouse hepatoma, B16 mouse melanoma, and Neuro 2A mouse neuroblastoma. The cytotoxicity of the corresponding di(8-quinolyl) diselenides **7** was determined separately (Table 4).

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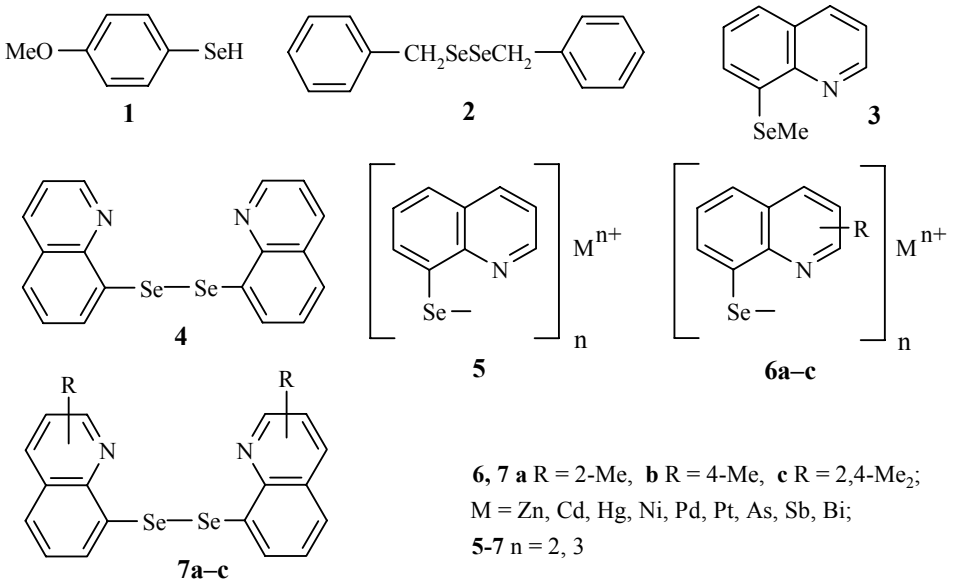

The results of the investigation showed that the cytotoxic activity of metal 8-quinolineselenolates depends on the nature of the ligand and on the metal. In a series of cases selectivity was displayed in relation to particular cell lines and also in the character of the action (action on cell membranes in the CV test; effect on the activity of mitochondrial enzymes in the MTT test).

In relation to HT-1080 human fibrosarcoma cells the cadmium(II) complex in the series of 2-methyl-8-quinolineselenol **6a** derivatives displayed the greatest cytotoxicity (in the CV and MTT tests). The mercury(II) complex proved to be somewhat less active, but they were both highly toxic in relation to normal BNK 21 kidney fibroblasts of the golden hamster and were toxic for normal NIH 3T3 mouse embryo fibroblasts. The palladium(II) complex was the most active of the group 12 metals. The complexes of the 15th group elements displayed high activity in the MTT test, depending on the element activity fell in the series As > Bi > Sb. Their 4-methyl-8-quinolyl derivatives **6b** proved to be significantly more active in both tests than the corresponding 2-methyl derivatives **6a**. The complexes of metals of the 10th and 12th groups with this same ligand were less active than the 2-methyl derivatives. In the series of 2,4-dimethyl derivatives **6c** a close dependence of activity on the nature of the metal was observed: Hg > Cd > Zn; As ≈ Bi >Sb; Pd > Ni. The most active of all the metal complexes with this ligand proved to be palladium(II) 2,4-dimethyl-8-quinolineselenolate. This complex, like the platinum complex, was less toxic in relation to normal NIH 3T3 cells.

In relation to MG-22A mouse hepatoma cells the greatest activity was displayed by the mercury(II) complex of the derivatives of 2-methyl-8-quinolineselenol. In the series of elements of the 15th group the sequence of reducing cytotoxicity was the same as in the case of HT-1080 cells, i.e. As > Bi > Sb.

The 4-methyl derivatives proved to be more active than the 2-methyl and 2,4-dimethyl derivatives. In difference to the 2-methyl derivatives the antimony(III) complex, containing a 4-methyl group in the quinoline ring, displayed greater cytotoxicity than the corresponding bismuth(III) derivatives. The palladium(II) complex with 4-methyl-8-quinolineselenol was more active than the platinum(II) selenolate and, possessing a good activity, was significantly less toxic in relation to normal NIH 3T3 cells. In the majority of cases the 2,4-dimethyl derivatives possessed a lower cytotoxicity than the corresponding 2- and 4-methyl derivatives. Exceptions were the cadmium(II) complex in the CV test and the platinum complex in the MTT test. The compounds of zinc(II) and nickel(II), as in the case of the 2-methyl derivatives, were the least active in their groups of elements.

TABLE 1. Cytotoxicity (IC_{50} μg/ml) of 2-Methyl-8-quinolineselenolates **6***

M	n	HT-1080		MG-22A		B16		Neuro2A		BHK 21		3T3
		CV	MTT	CV	MTT	CV	MTT	CV	MTT	CV	MTT	NR
Zn	2	35	54	19	28	1>>	0.5	1	0.5	*[2]	*[2]	*[2]
Cd	2	0.24	0.15	3	2.5	0.27	0.25	0.38	0.25	0.3	0.28	1
Hg	2	0.3	0.3	0.25	0.19	1>>	1>>	0.0007	0.003	0.006	0.003	1.2
Ni	2	10	*[3]	5	19	2	2	2	1	*[2]	*[2]	*[2]
Pd	2	1.7	1.5	3	3	2.2	1.6	0.5	0.25	0.3	0.24	2.7
Pt	2	10	22	1	2	2	2	1.6	1	*[2]	*[2]	*[2]
As	3	10	0.5	3	1.2	2	1	1.5	1.8	1.5	3.2	15
Sb	3	17	14	26	33	2.7	2.3	2.4	1.4	*[2]	*[2]	*[2]
Bi	3	4	0.85	3	3	1>>	1>>	5	6	3	3	3

* CV, crystal violet; MTT 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyl-2H-tetrazolium bromide; NR neutral red.

*[2] Not tested.

*[3] Cytotoxic effect absent.

TABLE 2. Cytotoxicity (IC_{50}, μg/ml) of 4-Methyl-8-quinolineselenolates **6b**

M	n	HT-1080		MG-22A		3H3	
		CV	MTT	CV	MTT	NR	LD_{50}, mg/kg
Cd	2	2.8	1.8	2.1	0.5	3	340
Hg	2	2.8	1.5	3	1	4	257
Pd	2	3	2.7	3	2.6	14	494
Pt	2	38	48	60	87	432	2230
As	3	0.4	1>>	1>>	1>>	3	295
Sb	3	0.5	1>>	0.2	2.2	5	392
Bi	3	3	1>>	2.4	2	5	349

TABLE 3. Cytotoxicity (IC_{50}, μg/ml) of 2,4-Dimethyl-8-quinoline-selenolates **6c**

M	n	HT-1080		MG-22A		3H3	
		CV	MTT	CV	MTT	NR	LD_{50}, mg/kg
Zn	2	13	20	24	25	5.5	310
Cd	2	3.5	3	0.3	1.5	2.8	239
Hg	2	2.7	0.4	6.4	9.8	3.8	295
Ni	2	22	16	16	21	5.4	302
Pd	2	0.4	1.1	11.4	10	26.3	634
Pt	2	1.5	3	2.8	0.5	14	525
As	3	2.6	2.8	2.8	2.5	2	207
Sb	3	12.6	18	20	27	24	621
Bi	3	2.6	2.7	14	17.5	10.6	469

TABLE 4. Cytotoxicity (IC_{50}, μg/ml) of Di(8-quinolyl) Diselenides **7**

Compound	R	HT-1080		MG-22A	
		CV	MTT	CV	MTT
[25]	H	0.8	2	3	2
7a	2-Me	6	18	38	10
7b	4-Me	0.6	0.8	1.4	2.7
7c	2,4-Me_2	*	*	*	*

* Cytotoxic effect absent.

All the complexes of 2-methyl-8-quinolineselenol studied were highly active in relation to B16 melanoma, particularly the derivatives of the 12th group metals and of bismuth(III), but they were also toxic in relation to normal BNK 21 and NIH 3T3 cells.

The mercury(II) complex possessed extremely high activity in relation to Neuro 2A mouse neuroblastoma cells. The remaining complexes also displayed high cytotoxicity to these cells. Their activity in groups of elements fell in the series Hg > Cd > Zn, Pd > Pt > Ni, and As > Sb > Bi.

From the data obtained it follows that the greatest cytotoxicity to HT-1080 cells was displayed by complexes of arsenic(III), antimony(III), and bismuth(III) with 4-methyl-8-quinolineselenol, and also complexes of cadmium(II) and mercury(II) with its 2-methyl isomer, to MG-22A cells by the compound of arsenic(III) with

a 4-methyl group, of mercury(II) with a 2-methyl group, and of cadmium(II) with 2,4-dimethyl-substituted 8-quinolineselenol, to B16 and Neuro 2A cells by mercury(II), cadmium(II), and zinc(II) 2-methyl-8-quinolineselenolate. All these compounds, while displaying high activity to tumor cells, are toxic to normal BNK-21 and NIH 3T3 cells.

The complexes of palladium(II) appeared to be more encouraging. They possessed a fairly high cytotoxicity towards tumor cells and were less toxic in relation to normal cells, particularly the 2,4-dimethyl derivatives. They displayed some selectivity in relation to various types of tumor cell. For the 2-methyl derivatives the cytotoxicity fell in the series Neuro 2A > HT-1080 > B16 > MG-22A, for the 2,4-dimethyl derivatives HT-1080 > B16 > Neuro 2A > MG-22A, and the toxicity to normal NIH 3T3 cells fell 2-Me > 4-Me > $2,4\text{-Me}_2$.

TABLE 5. Results of Elemental Analysis and Yields of 2-Methyl-8-quinolineselenolates **6a**

M	n	Found, % / Calculated, %			Yield, %
		C	H	N	
Zn	2	47.83 / 47.32	3.05 / 3.18	5.37 / 5.52	82
Cd	2	42.87 / 43.31	3.05 / 2.91	4.93 / 5.05	93
Hg	2	37.15 / 37.37	2.42 / 2.51	4.53 / 4.36	85
Ni	2	48.31 / 47.95	3.08 / 3.22	5.68 / 5.59	80
Pd	2	43.65 / 43.78	3.13 / 2.94	5.20 / 5.11	87
Pt	2	38.03 / 37.69	2.49 / 2.53	4.12 / 4.39	92
As	3	48.32 / 48.80	3.35 / 3.28	5.78 / 5.69	75
Sb	3	46.17 / 45.89	3.18 / 3.08	5.16 / 5.35	84
Bi	3	41.06 / 41.30	2.67 / 2.77	4.93 / 4.82	91

TABLE 6. Results of Elemental Analysis and Yields of 4-Methyl-8-quinolineselenolates **6b**

M	n	Found, % / Calculated, %			Yield, %
		C	H	N	
Cd	2	43.12 / 43.31	2.83 / 2.91	5.16 / 5.05	91
Hg	2	37.45 / 37.37	2.63 / 2.51	4.47 / 4.36	87
Pd	2	44.12 / 43.78	3.18 / 2.94	4.90 / 5.11	86
Pt	2	37.82 / 37.69	2.63 / 2.53	4.45 / 4.39	88
As	3	49.10 / 48.80	3.17 / 3.28	5.51 / 5.69	79
Sb	3	45.98 / 46.17	3.04 / 3.08	5.07 / 5.35	80
Bi	3	41.13 / 41.30	2.60 / 2.77	5.11 / 4.82	93

TABLE 7. Results of Elemental Analysis and Yields of 2,4-Dimethyl-8-quinolineselenolates **6c**

M	n	Found, % / Calculated, %			Yield, %
		C	H	N	
Zn	2	49.78 / 49.32	3.63 / 3.76	5.31 / 5.23	86
Cd	2	45.79 / 45.34	3.27 / 3.46	4.92 / 4.81	82
Hg	2	39.11 / 39.38	2.89 / 3.01	4.28 / 4.17	93
Ni	2	50.27 / 49.95	3.95 / 3.80	5.12 / 5.30	79
Pd	2	46.30 / 45.82	3.28 / 4.49	4.86 / 4.86	87
Pt	2	39.40 / 39.71	2.95 / 3.03	4.31 / 4.21	91
As	3	51.35 / 50.79	4.12 / 3.88	5.21 / 5.31	72
Sb	3	48.33 / 47.91	3.47 / 3.66	4.99 / 5.08	90
Bi	3	43.60 / 43.34	3.32 / 3.31	4.43 / 4.60	87

For comparison the cytotoxicity of the corresponding diquinolyl diselenides **7** were studied. The 4-methyl derivative **7b** proved to be the most active in relation to HT-1080 asnd MG-22A cells (more active than the unsubstituted diselenide [25]), while the 2,4-dimethyl derivative **7c** possessed no cytotoxicity.

EXPERIMENTAL

The elemental analyses were carried out with the aid of a CHN Analyser (Czechoslovakia).

2-Methyl-8-quinolineselenolates of Metals (6a). Compound **7a** [26] (0.1 g) was dissolved in 3 M hydrochloric acid (1 ml). Ethanol (5 ml) and 50% H_3PO_2 solution (0.5 ml) were added and the mixture left for 5 min. Saturated sodium acetate solution (2 ml) was added to the obtained solution of 2-methyl-8-quinolineselenol, and directly after mixing a solution of metal salt in water (2 ml) was added: $Zn(CH_3COO)_2 \cdot 2H_2O$ (0.045 g); $Cd(CH_3COO)_2 \cdot 2H_2O$ (0.055 g); $HgCl_2$ (0.055 g); $NiCl_2 \cdot 6H_2O$ (0.05 g); $PdCl_2$ (0.035 g); K_2PtCl_4 (0.08 g); As_2O_3 (0.013 g); $K(SbO)C_4H_4O_6 \cdot 0.5H_2O$ (0.045 g); $Bi(NO_3)_3 \cdot 5H_2O$ (0.065 g). In the case of the Pt salt the reaction mixture was heated on a water bath for 5 min. The obtained precipitate of metal 2-methyl-8-quinolineselenolate was filtered off, washed with water, dried in the air, and recrystallized from chloroform. The yields and results of elemental analyses of the complexes **6a** are given in Table 5.

4-Methyl-8-quinolineselenolates of Metals (6b) were obtained from di(4-methyl-8-quinolyl) diselenide **7b** [27] by the procedure given above. Yields and results of elemental analyses of complexes **6b** are given in Table 6.

2,4-Dimethyl-8-quinolineselenolates of Metals (6c) were obtained from di(2,4-dimethyl-8-quinolyl) diselenide **7c** [28] by an analogous procedure. Yields and results of elemental analyses of complexes **6c** are given in Table 7.

Cytotoxicity of the obtained compounds **6a-c** and of the initial diselenides **7** was determined by the procedure described in [25]. Their mean cytotoxic concentrations (IC_{50}, μg/ml) are given in Tables 1-4. The acute toxicity (LD_{50}, mg/kg) in a culture of 3T3 cells (alternative to LD_{50} in an *in vivo* test) was determined

according to the protocol of the Center for the Elaboration of Alternative Methods (NICEATM) of the Committee for the Validation of Alternative Methods (ICCVAM) and the National Program for Toxicology (NTP).

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