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# SYNTHESIS OF QUINOLINE-8-SELENOL, ITS COMPLEX COMPOUNDS WITH METALS AND THEIR CYTOTOXIC ACTIVITY

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*We have developed a novel method for synthesis of quinoline-8-selenol using selenourea instead of the previously used potassium selenocyanate. We have synthesized a series of metal quinoline-8-selenolates. We have studied the cytotoxic activity of the synthesized compounds against HT-1080, MG-22A, B16, Neuro 2A tumor cells. Mercury quinoline-8-selenolate is distinguished by high cytotoxicity for the three cell lines; the cadmium complex is most effective against B16 melanoma cells.*

**Keywords:** quinoline-8-selenol, metal quinoline-8-selenolates, cytotoxicity.

Organic and inorganic derivatives of selenium effectively inhibit growth of a number of tumors [1-6]. One of the mechanisms proposed to explain this effect is based on the cytotoxic effect of selenium on tumor cells [1, 7, 8].

In continuing our studies on the cytotoxicity of organoselenium compounds, we have synthesized metal complexes of quinoline-8-selenol and have studied their cytotoxicity against 4 lines of tumor cells.

Synthesis of quinoline-8-selenol from 8-aminoquinoline is described in the literature [9]. According to this method, 8-aminoquinoline undergoes diazotization and the diazonium salt is treated with potassium selenocyanate. The quinoline-8-selenolate obtained is hydrolyzed by hydrochloric acid in the presence of hypophosphorous acid, and quinoline-8-selenol is obtained in 12% yield.

We have developed a novel method for synthesis of quinoline-8-selenol, using selenourea instead of potassium selenocyanate, which made it possible to increase the yield of the target product up to 32%. The synthesis was carried out according to the Scheme 1.

8-Aminoquinoline (**1**) undergoes diazotization, and by treatment of the diazonium salt **2** with selenourea we obtain the quinoline-8-isoselenouronium derivative **3**, and by base hydrolysis of the latter in the presence of oxygen in the air 8,8'-diquinolyl diselenide (**4**) is formed, which is reduced by hypophosphorous acid in hydrochloric acid medium to form quinoline-8-selenol (**5**). In order to obtain pure 8,8'-diquinolyl diselenide, the quinoline-8-selenol is oxidized in alkaline medium by hydrogen peroxide. By treatment of quinoline-8-selenol with methyl iodide in alkaline medium, we obtain 8-methylselenoquinoline (**6**).

We obtained complex compounds (Table 1) by reaction of quinoline-8-selenol with metal salts.

We studied the cytotoxic activity of quinoline, 8-methylselenoquinoline (**6**), and compound **4**. Quinoline itself does not have cytotoxic activity; compound **6** exhibits weak cytotoxicity, while 8,8'-diquinolyl diselenide is significantly more active, especially with respect to HT-1080 cells (Table 2).

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Scheme 1

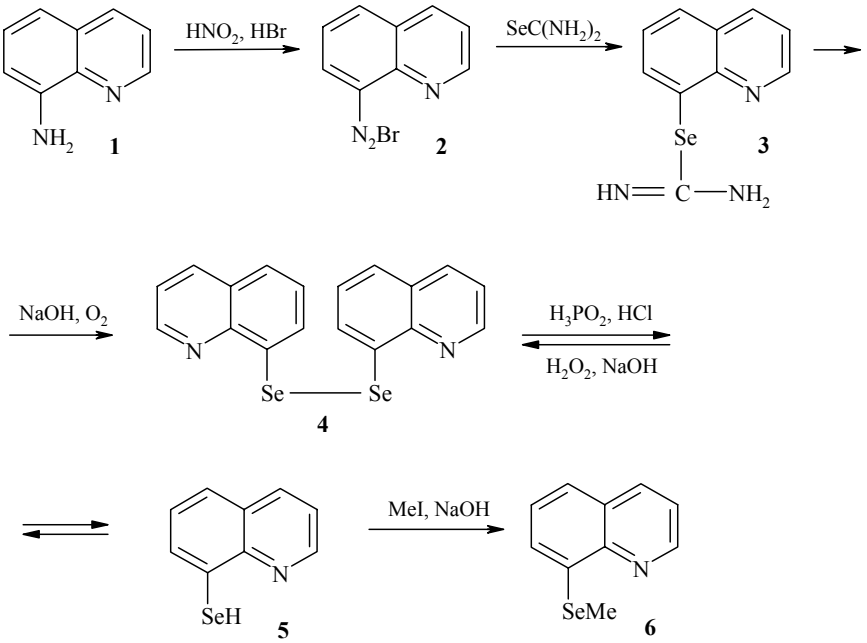


TABLE 1. Results of Elemental Analysis and Yields of Metal Quinoline-8-Selenolates

| Composition of complex | Found, % / Calculated, % | | | Yield, % |
|---|---|---|---|---|
| | C | H | N | |
| 1 | 2 | 3 | 4 | 5 |
| $Zn(C_9H_6NSe)_2$ | 45.73 / 45.08 | 2.68 / 2.52 | 5.72 / 5.84 | 86 |
| $Cd(C_9H_6NSe)_2$ | 41.36 / 41.05 | 2.15 / 2.30 | 5.58 / 5.32 | 84 |
| $Hg(C_9H_6NSe)_2$ | 34.98 / 35.16 | 2.07 / 1.97 | 4.37 / 4.56 | 87 |
| $Ga(C_9H_6NSe)_3$ | 47.37 / 46.93 | 2.56 / 2.62 | 6.19 / 6.08 | 75 |
| $In(C_9H_6NSe)_3$ | 44.03 / 44.05 | 2.57 / 2.46 | 5.83 / 5.71 | 85 |
| $Sn(C_9H_6NSe)_2$ | 41.62 / 40.57 | 2.14 / 2.27 | 5.23 / 5.26 | 83 |
| $Pb(C_9H_6NSe)_2$ | 35.52 / 34.79 | 1.84 / 1.95 | 4.63 / 4.51 | 83 |
| $As(C_9H_6NSe)_3$ | 46.12 / 46.58 | 2.43 / 2.61 | 5.87 / 6.03 | 74 |
| $Sb(C_9H_6NSe)_3$ | 44.11 / 43.64 | 2.62 / 2.44 | 5.78 / 5.65 | 83 |
| $Bi(C_9H_6NSe)_3$ | 39.12 / 39.06 | 2.25 / 2.18 | 5.17 / 5.06 | 75 |
| $VO(C_9H_6NSe)_2$ | 44.13 / 44.93 | 2.33 / 2.51 | 6.03 / 5.82 | 86 |
| $MoO_2(C_9H_6NSe)_2$ | 40.27 / 39.88 | 2.23 / 2.23 | 5.35 / 5.17 | 89 |
| $Cr(C_9H_6NSe)_3$ | 48.44 / 48.17 | 2.48 / 2.69 | 6.20 / 6.24 | 76 |
| $AgC_9H_6NSe$ | 34.67 / 34.32 | 2.12 / 1.92 | 4.58 / 4.45 | 93 |

TABLE 1 (continued)

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| $Pd(C_9H_6NSe)_2$ | 41.07 / 41.53 | 2.42 / 2.32 | 5.41 / 5.38 | 80 |
| $Pt(C_9H_6NSe)_2$ | 35.72 / 35.48 | 1.87 / 1.98 | 4.48 / 4.60 | 95 |
| $Rh(C_9H_6NSe)_3$ | 44.30 / 44.78 | 2.63 / 2.50 | 5.93 / 5.80 | 75 |
| $Ir(C_9H_6NSe)_3$ | 40.25 / 39.86 | 2.37 / 2.23 | 5.28 / 5.17 | 91 |
| $Ru(C_9H_6NSe)_3$ | 44.23 / 44.89 | 2.57 / 2.51 | 6.08 / 5.82 | 73 |
| $Os(C_9H_6NSe)_3$ | 40.53 / 39.96 | 2.05 / 2.23 | 5.34 / 5.18 | 89 |

TABLE 2. Cytotoxicity of Quinoline-8-Selenol Complexes, $IC_{50}$ (μg/ml)

| Nr. | Formula | HT-1080 | | MG-22A | | Neuro 2A | | B16 | |
|---|---|---|---|---|---|---|---|---|---|
| | | CV | MTT | CV | MTT | CV | MTT | CV | MTT |
| 1. | Quinoline | * | * | 28 | 65 | nt | nt | nt | nt |
| 2. | $C_{10}H_9Nse$ (VI) | 38 | 53 | 20 | 26 | nt | nt | nt | nt |
| 3. | $C_{18}H_{12}N_2Se_2$ (IV) | 0.8 | 2 | 3 | 2 | 5 | 1 | 7 | 24 |
| 4. | $AgC_9H_6NSe$ | 100 | 32 | 53 | 59 | 26 | 12 | nt | nt |
| 5. | $Pd(C_9H_6NSe)_2$ | 2 | 4 | 6 | 12 | nt | nt | nt | nt |
| 6. | $Pt(C_9H_6NSe)_2$ | 68 | 100 | * | * | nt | nt | nt | nt |
| 7. | $Zn(C_9H_6NSe)_2$ | 1 | 3 | 3 | 2 | 12 | 22 | 33 | 34 |
| 8. | $VO(C_9H_6NSe)_2$ | 2 | 2 | 3 | 4 | 3 | 2 | 1 | 1 |
| 9. | $MoO_2(C_9H_6NSe)_2$ | 3 | 3 | 3 | 3 | 3 | 2 | 3 | 1 |
| 10. | $Cd(C_9H_6NSe)_2$ | 3 | 3 | 3 | 3 | 3 | 2 | << 1 | << 1 |
| 11. | $Hg(C_9H_6NSe)_2$ | << 1 | << 1 | 0.011 | 0.029 | << 1 | << 1 | 3 | 10 |
| 12. | $Sn(C_9H_6NSe)_2$ | 3 | 2 | 2 | 3 | 3 | 2 | 1 | 1 |
| 13. | $Pb(C_9H_6NSe)_2$ | 2 | 3 | 2 | 3 | 2 | 1 | 1 | 3 |
| 14. | $Cr(C_9H_6NSe)_3$ | * | 34 | * | * | nt | nt | nt | nt |
| 15. | $Sb(C_9H_6NSe)_3$ | 3 | 2 | 1 | 3 | 6 | 11 | 4 | 7 |
| 16. | $In(C_9H_6NSe)_3$ | 0.4 | 0.6 | 3 | 3 | 3 | 6 | 8 | 3 |
| 17. | $Ga(C_9H_6NSe)_3$ | 3 | 1 | 3 | 1 | 3 | 2 | 1 | 3 |
| 18. | $As(C_9H_6NSe)_3$ | 1 | 2 | 3 | 3 | 3 | 1 | 1 | 1 |
| 19. | $Bi(C_9H_6NSe)_3$ | 3 | 3 | 3 | 4 | 3 | 2 | 1 | 1 |
| 20. | $Rh(C_9H_6NSe)_3$ | 15 | 46 | 36 | 23 | 13 | 14 | 13 | 12 |
| 21. | $Ir(C_9H_6NSe)_3$ | 16 | 6 | 28 | 11 | 16 | 14 | nt | nt |
| 22. | $Ru(C_9H_6NSe)_3$ | 5 | 2 | 8 | 8 | 4 | 2 | 1 | 1 |
| 23. | $Os(C_9H_6NSe)_3$ | 2 | 2 | 2 | 2 | 3 | 1 | * | 11 |

* No cytotoxic effect; nt = not tested.

Among the quinoline-selenol complexes, the mercury(II) complex has high cytotoxicity against all the studied tumor cell lines. Its $IC_{50}$ against MG-22A mouse hepatoma cells was 0.011 (CV) and 0.029 μg/ml (MTT). The cadmium(II) complex proved to be the most active with respect to B16 melanoma cells, while the indium(III) complex exhibited the greatest cytotoxicity against HT-1080 human lung fibrosarcoma cells. The arsenic(III), zinc(II), gallium(III), and osmium(III) complexes also were active against these cells. It is interesting that the osmium derivative is not effective against B16 melanoma, but is highly toxic for normal

cells. The gallium(III) complex is active against MG-22A cells. Antimony(III) and osmium(III) complexes also exhibited high cytotoxicity against these cells. The lead(II), tin(II), and bismuth(III) complexes are effective against both Neuro 2A and B16 melanoma.

The data obtained allow us to assess the effect of the nature of the metal in the quinoline-8-selenol complexes on their cytotoxicity and selectivity of action, which is necessary in order to search further for compounds that are the most cytotoxic for tumor cells and the least harmful for normal cells.

## EXPERIMENTAL

Elemental analyses were done using an Analyser CHN analyzer (Czechoslovakia). The UV spectra were recorded on a Specord UV-vis spectrophotometer (Carl Zeiss, Jena).

**8,8'-Diquinolyl Diselenide (4).** 8-Aminoquinoline (5.0 g) was dissolved in a mixture of 40% hydrobromic acid (25 ml) and water (80 ml). The mixture was cooled down in an ice bath to +2°C, and a solution of sodium nitrite (2.4 g) in water (20 ml) was poured in. The solution was stirred for 5 min and then a solution of selenourea (5 g) in water (100 ml) was added, and the mixture was heated for 1 h on a water bath at 70°C. Water (200 ml) was added to the red solution of the quinoline-8-isoselenouronium derivative, the mixture was cooled down to room temperature, and a 30% NaOH solution was added until it tested alkaline. The mixture was allowed to stand for 1 h in air, occasionally transferring it from one beaker to another to promote oxidation of the quinoline-8-selenol by the oxygen in the air. Then the solution was filtered and the precipitate was dissolved in a mixture of hydrochloric acid (1:1) (15 ml) and a 50% solution of hypophosphorous acid ($H_3PO_2$) (5 ml), and heated for 5 min on a water bath. Then the solution was diluted with argon-saturated water (400 ml), a 30% NaOH solution was added until it tested alkaline, and it was filtered. A 10% hydrogen peroxide solution was added to the filtrate until precipitation was complete. The colorless precipitate was filtered out, washed with water, and dried in air. The reduction and oxidation procedure was repeated to purify compound **4**. Yield of diselenide **4** 2.3 g (32%); mp 205°C. UV spectrum in chloroform: $\lambda_1$ = 251 nm, $\lambda_2$ = 335 nm, $\varepsilon_1$ = 38 000, $\varepsilon_2$ = 9600. Found, %: C 52.63; H 2.72; N 6.91. $C_{18}H_{12}N_2Se_2$. Calculated, %: C 52.19; H 2.92; N 6.77.

**Quinoline-8-selenol (5).** Compound **4** (0.5 g) was dissolved in hydrochloric acid (1:1) (2 ml), a 50% $H_3PO_2$ solution (2 ml) and water (5 ml) were added, and it was allowed to stand for 10 min. Then water (20 ml) and a saturated sodium acetate solution (10 ml) were added. The precipitated dark-red material was filtered out, washed with water, saturated with argon, and dried above KOH in a desiccator filled with argon. Yield of compound **5** 0.35 g (70%). Compound **5** is oxidized in air over the course of a few days to form the colorless compound **4**, but is rapidly oxidized upon heating; so we could not determine its melting point. Found, %: C 52.43; H 3.47; N 6.58. $C_9H_7NSe$. Calculated, %: C 51.94; H 3.39; N 6.73.

**8-Methylselenoquinoline (6)**. Compound **4** (0.5 g) was dissolved in hydrochloric acid (1:1) (2 ml), then a 50% $H_3PO_2$ (2 ml) solution and water (5 ml) were added and it was allowed to stand for 10 min. Then ethanol (20 ml) and methyl iodide (0.2 ml) were added along with a 30% NaOH solution until the color of the solution changed from dark-red to light-yellow. Then the solution was gradually diluted with water up to 100 ml. The precipitated light-yellow crystalline precipitate was filtered out, washed with water, and dried in air. Yield of compound **6** 0.39 g (73%); mp 60°C. UV spectrum in chloroform: $\lambda_1$ = 259 nm, $\lambda_2$ = 345 nm, $\varepsilon_1$ = 16 800, $\varepsilon_2$ = 4600. Found, %: C 53.12; H 3.87; N 6.52. $C_{10}H_9NSe$. Calculated, %: C 54.07; H 4.08; N 6.31.

**Synthesis of Metal Quinoline-8-selenolates** (Table 1). Compound **4** (0.5 g) was dissolved in 3M hydrochloric acid (4 ml), then ethanol (10 ml) and a 50% $H_3PO_2$ solution (2 ml) were added and the mixture was allowed to stand for 10 min. Then a saturated sodium acetate solution (7 ml) was added to the solution of quinoline-8-selenol obtained, and then a solution of the metal salt in water (5 ml) was immediately added with stirring: 0.25 g $Zn(CH_3COO)_2 \cdot H_2O$; 0.3 g $Cd(CH_3COO)_2 \cdot 2H_2O$; 0.3 g $HgCl_2$; 0.16 g $Ga_2(SO_4)_3$; 0.25 g $In_2(SO_4)_3 \cdot 7H_2O$; 0.25 g $SnCl_2 \cdot 2H_2O$; 0.35 g $Pb(NO_3)_2$; 0.12 g $Na_2HAsO_3$; 0.25 g $K(SbO)C_4H_4O_6 \cdot 0.5H_2O$;

0.35 g $Bi(C_4H_4O_6)3\cdot 6H_2O$; 0.24 g $VOSO_4\cdot 3H_2O$; 0.27 g $Na_2MoO_4\cdot 2H_2O$; 0.37 g $KCr(SO_4)_2\cdot 12H_2O$; 0.39 g $AgNO_3$; 0.2 g $PdCl_2$; 0.5 g $K_2[PtCl_4]_2$; 0.15 g $RhCl_3$; 0.39 g $(NH_4)_3[IrCl_6]$; 0.27 g $K_2[Ru(H_2O)Cl_5]$; 0.56 g $K_2[OsBr_6]$. In the case of Pt, Rh, Ir, Ru, Os, and Cr salts, the reaction mixture was heated for 5 min on a water bath. The precipitate of metal quinoline-8-selenolates obtained was filtered out, washed with water, dried in air, and recrystallized from chloroform.

**Determination of cytotoxicity.** The cytotoxic effect of the compounds was tested on monolayer cultures of HT-1080 (human fibrosarcoma), MG-22A (mouse hepatoma), B16 (mouse melanoma), Neuro 2A (mouse neuroblastoma). The cells were cultured in Sigma DMEM medium without phenol red or antibiotics and with 5% Sigma fetal serum. After thawing, ampules were used with only 1-4 passages of the cell cultures, 2-5 × 104 cells/ml depending on the cell culture used; they were added to a 96-well plate to which the drug had already been added. The control cells without the drug were cultured on a separate plate. The cells were cultured for 72 h at 37°C in 5% $CO_2$. The number of live cells was determined by staining with crystal violet (CV), from the integrity of the cell membranes and from staining with MTT [3-(4,5-dimethylthiazole-2,5-diphenyltetrazolium bromide)], from the activity of mitochondrial enzymes in the cell. The number of cells on the control plate was taken as 100% [10]. The median inhibitory concentration ($IC_{50}$) of the quinoline-8-selenol complexes is given in Table 2.

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