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SYNTHESIS AND RADIOPROTECTIVE EFFECTS OF DERIVATIVES OF THIADIAZOLES, DITHIOLIDENES, AND THEIR SELENIUM ANALOGS

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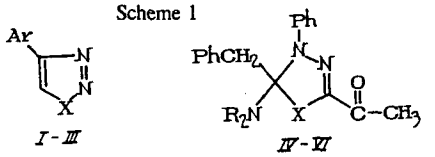
Derivatives of the sulfur-containing five-membered heterocyclic ring compounds, the 1,2,3-thiadiazoles, 1,3,4-thioadiazole, and 1,3-dithio-2-ylidenes, have a wide spectrum of biological activity [1]. Studies of the radioprotective effects of sulfur-containing five-membered heterocyclic ring compounds have revealed such properties among a number of thiazoles [2]. A number of heterocyclic selenium derivatives have also been shown to have radioprotective properties [2].

We report here the synthesis and study of the toxic and radioprotective properties of 4-aryl-1,2,3-thia(selena)diazoles (compounds I-III), 2-dialkylamino-1,3,4-thia(selena)diazolines (IV-VI), 2-benzylidene-1,3,4-thia(selena)diazolines (VII, VIII), and 2-arylidene-1,3-dithio(seleno)ols (IX-XI).

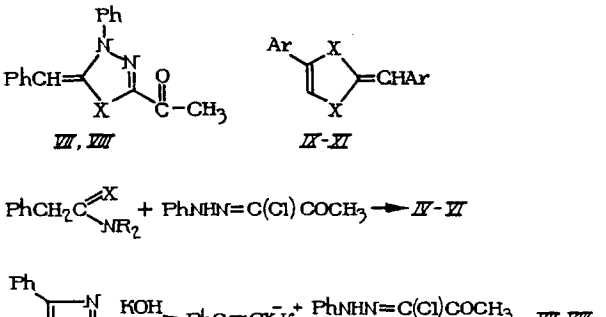
Scheme 1



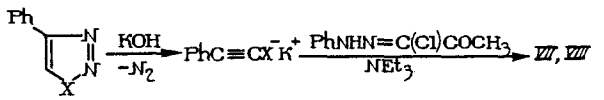
I-III IV-VI

Ar=p-BrC_6H_4 (I), p-ClC_6H_4 (II, III); X=S (I, II), Se (III).
NR_2=$N(CH_2)_5$ (IV, V), $N(CH_2CH_2)_2O$ (VI);
X=S (IV), Se (V, VI).

Scheme 2



VII, VIII IX-XI



Ar=p-ClC_6H_4 (IX), p-$CH_3C_6H_4$ (X, XI), X=S (VII, IX, X).
Se (VIII, XI).

The compounds studied (I-XI) are not only similar in terms of the cyclic system (five-membered unsaturated sulfur- or selenium-containing heterocyclic rings), but also in terms of their synthesis. Thus, 1,2,3-thia(selena)diazoles I-III were prepared from arylmethylketone hydrazones by treatment with $SOCl_2$ and SeO_2 using previously known methods [3, 4]. In turn, heterocycles I-III were the starting compounds for the synthesis of compounds IV-XI. Compounds I-III were treated with KOH

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TABLE 1. UV, IR, and PMR Spectra of Compounds I, IV-VIII, and XI:

Compound	UV spectrum, λ_{max}, nm (log ε)	IR spectrum, ν_{max}, cm^{-1}	PMR spectrum, δ, ppm
I	256(4,19)	3115, 2990, 1600, 1450, 1220, 1075, 1007, 932, 892, 830, 805, 715	7.95-7.20, m (4H arom.), 8.45 s (1H)
IV	246(4,01), 280(3,05), 3,49(4,15)	2980, 2860, 1680, 1600, 1530, 1500, 1445, 1260, 1175, 1118, 973, 817, 760	1.55 m (6H), 2.15 s (3H), 2.55 m (4H), 3.40 d (1H), 3.60 d (1H), 6.80-7.70 m (10H arom)
V	248(4,05), 282(3,62), 3,75(4,03)	2930, 1680, 1600, 1530, 1500, 1460, 1390, 1235, 1150, 1030, 900, 760, 700	1.15 m (6H), 1.90 s (3H), 2.15 m (4H), 3.02 d (1H), 3.74 d (1H), 6.80-7.60 m (10H arom)
VI	240(4,03), 282(3,59), 367(3,98)	2990, 2960, 1670, 1605, 1525, 1500, 1470, 1370, 1300, 1280, 1260, 1180, 1136, 1115, 980, 909, 878, 755, 703	2.02 s (3H, CH_3CO), 2.18 m (4H, CH_2NCH_2), 3.08 d (1H, CH_2), 3.48 m (5H, CH_2 + CH_2OCH_2), 7.0-7.40 m (10H arom)
VII	315(4,12), 441(3,76)	2995, 2930, 1666, 1584, 1566, 1530, 1488, 1260, 1164, 1156, 768, 704	2.40 s (3H), 6.0 s (1H), 7.0-7.40 m (10H arom)
VIII	235(3,86), 332(4,06), 4,44(3,83)	2990, 2975, 2930, 1675, 1605, 1580, 1560, 1495, 1357, 1208, 1141, 1005, 950, 827, 788, 696	2.43 s (3H), 6.05 s (1H), 7.20-7.58 m (10H arom)
XI	251(3,63), 350(3,50)	3030, 2930, 2865, 1640, 1580, 1513, 1490, 1410, 1283, 1130, 863, 850, 812	2.10 d (6H), 6.90-7.60 m (8H arom + 2H)

in the presence of secondary amines, initially as described in [5], giving thio(seleno)amides of phenylacetic acid. Subsequent treatment of the resulting thio(seleno)amides with hydrazolyl chloride in the presence of K_2CO_3 and $\overset{+}{N}(Bu)_4\bar{B}r$ yielded the desired 1,3,4-thia(selena)diazolines (V-VI).

Synthesis of compounds VII and VIII, and IX and XI was also carried out starting with 1,2,3-thia(selena)diazoles. Treatment with KOH as described in [6] yielded the corresponding potassium salts of the ethinthiols and selenols, and treatment of these with hydrazonoyl chlorides in the presence of NEt_3 converted them into compounds VII and VIII, with good yields.

In turn, HCl was used to treat these ethinthiolates and selenolates as described in [7], to produce 2-arylydene-1,3-dithiols(selenols) IX-XI.

The structures of all newly synthesized heterocyclic compounds I, IV-VIII, and XI were confirmed by UV, IR, and PMR spectra (Table 1). Elemental analysis agreed with predicted data. The properties and yields of the compounds synthesized are shown in Table 2. The properties of compounds II and III, and IX and X agreed with previously published data [3, 4, 7].

EXPERIMENTAL (CHEMICAL)

UV spectra were taken on an SF-4A spectrophotometer using ethanol solutions. IR spectra were taken on a UR-20 spectrophotometer in KBr, and PMR spectra were taken on a Tesla BS-480 (100 MHz) apparatus as 3-10% solutions in CCl_4, using HMDS as the internal standard. The PMR spectrum of compound XI was taken as a 3% solution in DMSO. The phenylhydrazolyl chloride of pyruvic acid was prepared as described in [8].

2-Benzyl-2-piperidino-3-phenyl-5-acetyl-1,3,4-thiadiazoline (IV). K_2CO_3 (1 g) was added to a solution containing 2.5 mmole of N-(phenylthioacetyl)piperidine [5] and 0.2 g of $\overset{+}{N}Bu_4.\bar{B}r$ in 5 ml of benzene, and then a solution of 2.55 mmole of the phenylhydrazonoyl chloride of pyruvic acid in 5 ml of benzene was added dropwise over 30 min with intense mixing at room temperature. After incubation for 30 min, the reaction mixture was filtered, and the solvent was evaporated in vacuo. The residue was taken up in 10 ml of ethanol and the dark cherry-colored solution was cooled to 0°C. The resulting light yellow powder was collected by filtration. Compound IV was obtained after recrystallization.

2-Benzyl-2-piperidino-3-phenyl-5-acetyl-1,3,4-selenadiazoline (V). This was prepared by the same method as used for compound IV, from N-(phenylselenoacetyl)piperidine [5].

2-Benzyl-2-morpholino-3-phenyl-5-acetyl-1,3,4-selenadiazoline (VI). This was prepared by the same method as used for compound IV, from N-(phenylselenoacetyl)morpholine [5].

2-Benzylidene-3-phenyl-5-acetyl-1,3,4-thiadiazoline (VII). Small portions of freshly-prepared potassium 2-phenylethinthioate [6] were added to a solution of 10 mmole of the phenylhydrazonoyl chloride of pyruvic acid and 20 mmole of NEt_3 in 100 ml of absolute benzene, under a dry argon atmosphere. The mixture was stirred at room temperature for 2 h and incubated overnight. The resulting precipitate of KCl was removed by filtration and the filtrate was dried in vacuo. Recrystallization of the residue yields compound VII.

TABLE 2. Properties of Compounds I-XI

Compound	Yield, %	Melting temperature, °C	Solvent for crystallization	Empirical formula
I	78	150—2	CCl_4	$C_8H_5BrN_2S$
II*	72	137—9	Benzene	$C_8H_5ClN_2S$
III**	65	130—1	Chloroform	$C_8H_5ClN_2Se$
IV	83	116—8	Benzene—heptane (1:1)	$C_{22}H_{25}N_3OS$
V	90	139—40	Hexane	$C_{22}H_{25}N_3OSe$
VI	90	146—8	»	$C_{21}H_{23}N_3O_2Se$
VII	86	144—5	Ethanol	$C_{17}H_{14}N_2OS$
VIII	82	145—6	»	$C_{17}H_{14}N_2OSe$
IX***	90	239—41	DMSO	$C_{16}H_{10}Cl_2S_2$
X*4	96	228—9	DMSO	$C_{18}H_{16}S_2$
XI	93	155—6	Ethanol	$C_{18}H_{16}Se_2$

*Melting point 137-9°C [3].

**Melting point 129-31°C [4].

***Melting point 239-41°C [7].

*4Melting point 228-9°C [7].

2-(*p*-Methylbenzylidene)-4-(*p*-tolyl)-1,3-diselenol (XI). Dioxane (50 ml) was added to a solution of 10 mmole of KOH in 2 ml of absolute ethanol, followed by 10 mmole of 4-(*p*-tolyl)-1,3,3-selenadiazole [4]. After nitrogen emission had stopped and the reaction had been incubated for 30 min, it was poured into 100 ml of water. The resulting precipitate was collected by filtration. Compound XI was obtained after recrystallization of the residue.

EXPERIMENTAL (BIOLOGICAL)

Studies of the toxic and radioprotective properties of heterocyclic compounds I-XI were carried out on F_1(CBA × C57B1) mice of both sexes, weighing 18-22 g, and kept on a standard diet, according to the tactical-technical and medical-biological requirements for the experimental and clinical study of radioprotective agents [9]. Each dose was given to five mice, and observations were continued for three days.

All substances were insoluble in water, so were used as suspensions in 1% solutions of tween-80. Suspensions were given i.p. as doses of 0.1 ml per 10 g of weight. When very thick suspensions were obtained, the volume of tween used for preparation of suspensions was doubled, and doses of 0.2 ml per 10 g were used. The results were analyzed statistically using the Litchfield and Wilcoxon method [10]. For toxic compounds, doses killing 16%, 50%, and 84% of animals (LD_{16}, LD_{50}, and LD_{84}) were calculated.

The radioprotective properties of compounds III, IV, VII-IX, and XI were studied by irradiating mice using an RUM-1 x-ray apparatus with a dose of 850 rad, a Cu (0.5 mm) + Al (1 mm) filter, a radiation rate of 450 rad/min, and a focusing distance of 17 cm. For toxic compounds, the radioprotective effect was tested at doses of 1/8 and 1/2 LD_{16}, while doses of 50 and 500 μmole/kg were used of non-toxic compounds.

Each dose was tested on 10 mice, and compounds were given 15 min before irradiation. Two controls were carried out, i.e. radiation after dosage with physiological saline or 1% tween (n = 6), and irradiation after dosage with the widely used radioprotector mesatone (10 mg/kg; n = 6). Observations were continued for 30 days after irradiation. The suitability of the experiment was confirmed by the efficacy of mesatone, which was close to 100%, as well as the 100% lethality in the biological control over 30 days ($LD_{100/30}$).

Studies of the toxicity of all compounds was hindered by their complete insolubility in water. Toxic doses of compounds I, IV, and IX could not be achieved over the dose range 100-1000 mg/kg. The maximum tested doses of compounds VII, VIII, and XI were even lower, at 500 mg/kg. Very thick suspensions were obtained at levels of over 500 mg/kg.

Toxicity and radioprotection results are shown in Table 3. The first group of substances (I-III) were characterized by the presence of a heteroatom in the ring (S and Se), along with a substituent in the phenyl radical (Cl and Br). Substitution

TABLE 3. Biological Properties of Heterocyclic Compounds I-XI

Compound	Toxicity (LD_{50}), mg/kg	Doses used for irradiation, mg/kg	Radioprotective effect, %
I	0	—	—
II	390	—	—
III	51,5	3,2	0
		12,7	0
IV	0	18,9	0
		189	0
V	345	—	—
VI	253	—	—
VII	0	14,7	0
		147	0
VIII	0	17	0
		170	0
IX	0	16,8	0
		168	30
X	0	—	—
XI	1012	19,5	0
		195	0

of the bromine atom in the phenyl radical (I) for a chlorine atom (II) led to the appearance of toxicity. Substitution of the sulfur heteroatom in the rings of I and II with selenium (III) gave a sharp increase in toxicity, and the LD_{50} decreased about eight fold.

Substances of the second group (IV-VI) were also characterized by the heteroatom in the ring (S and Se) and one of the radicals (piperidine or morpholine). Substitution of sulfur in the ring with selenium in V led to the appearance of toxicity in compound V. Additional substitution of the piperidine radical with the morpholine radical somewhat increased the toxicity of VI, reducing the toxic dose about 1.5 fold.

We were unable to demonstrate a relationship between the toxicity and the presence of the selenium atom for compounds VII and VIII (third group). The maximum dose tested was 500 mg/kg, and toxicity was not obtained.

The main difference in the fourth group (IX-XI) was also in the heteroatom in the ring. Introduction of a selenium atom into the ring in place of the sulfur atom led to the appearance of toxicity in compound XI, though at a fairly high dose (LD_{50} = 1012 mg/kg).

The results on radioprotective properties showed that these compounds lacked such properties at the doses used, with the exception of compound IX at a dose of 500 μmole/kg.

Thus, these studies of the toxicity and radioprotective effects have demonstrated a relationship between the toxicity of heterocyclic compounds I-XI and the presence of a selenium atom in the ring, without finding radioprotective properties among these five-membered, sulfur-, selenium-, and nitrogen-containing heterocyclic ring compounds, with the exception of 2-arylidene-1,3-dithiol (IX).

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