Selenium Heterocycles XXII: Synthesis and Antibacterial and Antifungal Activities of Arylsulfonyl-1,2,3-selenadiazoles

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Received September 12, 1977, from the *Department of Chemistry and the Department of Industrial Pharmacy, College of Pharmacy, Tehran University, Tehran, Iran.* Accepted for publication January 11, 1978.

Abstract □ Series of 4-arylsulfonylmethyl-1,2,3-selenadiazoles, 4-(1-arylsulfonylethyl)-1,2,3-selenadiazoles, and 4-alkyl (or aryl) -5-arylsulfonyl-1,2,3-selenadiazoles were synthesized. 4-(3-Pyridyl)-5-phenylsulfonyl-1,2,3-selenadiazole exhibited the highest activity of growth inhibition against some bacteria and fungi.

Keyphrases □ 1,2,3-Selenadiazoles, various substituted—synthesized, antibacterial and antifungal activities evaluated □ Antibacterial activity—various substituted 1,2,3-selenadiazoles evaluated □ Antifungal activity—various substituted 1,2,3-selenadiazoles evaluated □ Structure–activity relationships—various substituted 1,2,3-selenadiazoles evaluated for antibacterial and antifungal activities

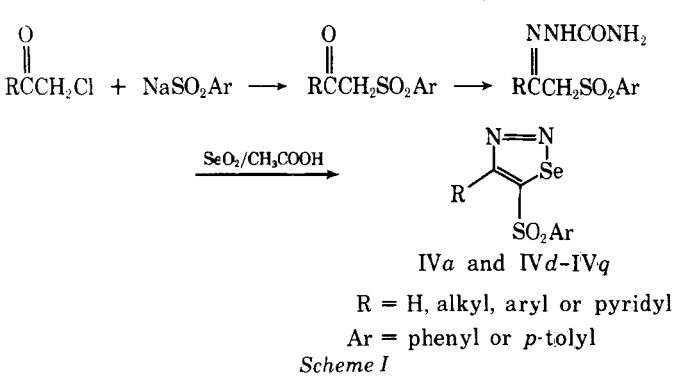
Recently, the antibacterial activity of series of 4-pyridyl-1,2,3-thiadiazoles, 4-pyridyl-1,2,3-selenadiazoles, and related 1,4-diselenafulvenes was reported (1). However, 4-substituted (1,2,3-selenadiazol-5-yl)carbamic acid esters and their sulfur analogs did not show significant antibacterial activity (2). Similarly, although selenosemicarbazide and its acyl derivatives exhibited potent antibacterial activity, the corresponding sulfur analogs were inactive (3).

The purpose of the present work was to study the influence of the sulfone group on the antibacterial and antifungal activities of the 1,2,3-selenadiazole ring system.

DISCUSSION

Chemistry—The selenium dioxide oxidation of the appropriate α-methyl or methylene aldehyde or ketone semicarbazones, as described previously (4–6), was used for the synthesis of arylsulfonyl-1,2,3-selenadiazoles. Chloroacetaldehyde or the appropriate α-chloroketones were condensed with sodium salts of benzenesulfinic acid or *p*-toluenesulfinic acid to give the desired carbonyl compounds (Scheme I). Semicarbazones of the carbonyl compounds reacted with selenium dioxide in hot acetic acid to afford the corresponding 1,2,3-selenadiazoles IV*a*, IV*d*–IV*q* (Scheme I), IV*b*, IV*c*, V*a*, V*b* (Scheme II), and V*c* (Scheme III). With the acetonylarylsulfonylsemicarbazones, isomeric 1,2,3-selenadiazoles V*a*–IV*b* and V*b*–IV*c* were obtained. In both cases, the isomers were separated easily by repeated crystallization (Scheme II).

All other 1,2,3-selenadiazoles were prepared similarly. With the 4-pyridyl-1,2,3-selenadiazoles, the reaction mixture was neutralized and

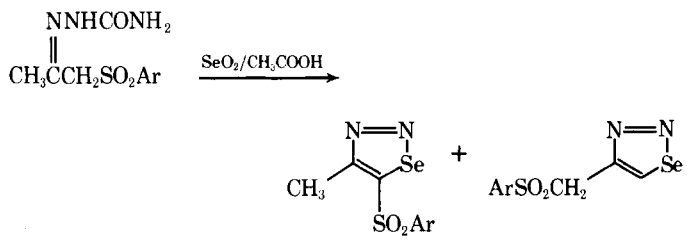


IV*a* and IV*d*–IV*q*

R = H, alkyl, aryl or pyridyl

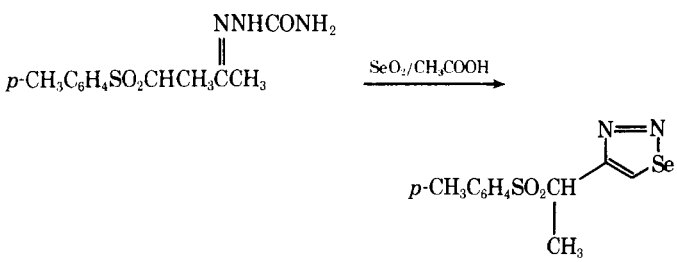
Ar = phenyl or *p*-tolyl

Scheme I



IV*b* and IV*c* V*a* and V*b*

Scheme II



V*c*

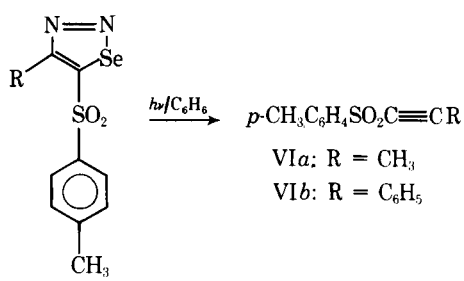
Scheme III

the crude compounds were purified by crystallization from aqueous ethanol. All 1,2,3-selenadiazoles prepared are listed in Table I.

An attempt to prepare arylsulfonylacetylenes by mild pyrolysis of arylsulfonyl-1,2,3-selenadiazoles failed. However, photolysis of 4-methyl-5-*p*-toluenesulfonyl-1,2,3-selenadiazole (IV*c*) and 4-phenyl-5-*p*-toluenesulfonyl-1,2,3-selenadiazole (IV*e*) in benzene afforded good yields of the corresponding acetylenes, VI*a* and VI*b* (Scheme IV). Compounds unsubstituted at the 5-position polymerized with these conditions and did not lead to the formation of the desired acetylenes.

Mass spectra of 5-unsubstituted 1,2,3-selenadiazoles showed a very weak parent molecular ion, and an M − SO_2 fragment was common in these molecules. 4,5-Disubstituted compounds also had a very weak parent molecular ion, and the base peak was M − (SO_2 + N_2). Ions corresponding to the arylacetylenes existed in both series.

Biological Activity—Compounds listed in Table II were tested against *Bacillus subtilis* (NCTC 3910), *Sarcina lutea* (ATCC 9341), *Staphylococcus aureus* (ATCC 6538), and *Escherichia coli* (ATCC 4352). Nitrofurazone was used as the control. The compounds were dissolved in pure acetone and diluted to 1% (w/v). Standard paper disks of 6-mm



VI*a*: R = CH_3

VI*b*: R = C_6H_5

IV*c* and IV*e*

Scheme IV

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Table I—Arylsulfonyl-1,2,3-selenadiazoles

Compound	R	Ar	Yield, %	Melting Point	Formula	Analysis, %	Calc.	Found
IV*a*	H	*p*-$CH_3C_6H_4SO_2$	48	129–131°	$C_9H_8N_2O_2SSe$	C	37.63	37.71
						H	2.78	2.80
IV*b*	CH_3	$C_6H_5SO_2$	63	76–78°	$C_9H_8N_2O_2SSe$	C	37.63	37.56
						H	2.78	2.75
IV*c*	CH_3	*p*-$CH_3C_6H_4SO_2$	56	64–65°	$C_{10}H_{10}N_2O_2SSe$	C	39.86	39.68
						H	3.32	3.28
IV*d*	C_6H_5	$C_6H_5SO_2$	38	163–165°	$C_{14}H_{10}N_2O_2SSe$	C	48.13	48.21
						H	2.86	2.78
IV*e*	C_6H_5	*p*-$CH_3C_6H_4SO_2$	76	130–135°	$C_{15}H_{12}N_2O_2SSe$	C	49.56	49.77
						H	3.30	3.33
IV*f*	*p*-ClC_6H_4	*p*-$CH_3C_6H_4SO_2$	59	110–115°	$C_{15}H_{11}ClN_2O_2SSe$	C	45.28	45.33
						H	2.76	2.69
IV*g*	*p*-BrC_6H_4	*p*-$CH_3C_6H_4SO_2$	66	108–113°	$C_{15}H_{11}BrN_2O_2SSe$	C	40.72	41.01
						H	2.48	2.53
IV*h*	*m*-$NO_2C_6H_4$	$C_6H_5SO_2$	53	125–128°	$C_{14}H_9N_3O_4SSe$	C	42.63	42.50
						H	2.28	2.30
IV*i*	*p*-$NO_2C_6H_4$	$C_6H_5SO_2$	46	130–135°	$C_{14}H_9N_3O_3SSe$	C	42.63	42.77
						H	2.28	2.31
IV*j*	*m*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4SO_2$	79	128–132°	$C_{15}H_{11}N_3O_4SSe$	C	44.11	44.12
						H	2.69	2.75
IV*k*	*p*-$NO_2C_6H_4$	*p*-$CH_3C_6H_4SO_2$	77	164–166°	$C_{15}H_{11}N_3O_4SSe$	C	44.11	44.20
						H	2.69	2.68
IV*l*	2-Pyridyl	$C_6H_5SO_2$	60	107–110°	$C_{13}H_9N_3O_2SSe$	C	44.57	44.68
						H	2.57	2.61
IV*m*	3-Pyridyl	$C_6H_5SO_2$	63	75–77°	$C_{13}H_9N_3O_2SSe$	C	44.57	44.59
						H	2.57	2.39
IV*n*	4-Pyridyl	$C_6H_5SO_2$	61	161–165°	$C_{13}H_9N_3O_2SSe$	C	44.57	44.44
						H	2.57	2.60
IV*o*	2-Pyridyl	*p*-$CH_3C_6H_4SO_2$	76	118–120°	$C_{14}H_{11}N_3O_2SSe$	C	46.15	46.10
						H	3.02	2.98
IV*p*	3-Pyridyl	*p*-$CH_3C_6H_4SO_2$	78	139–140°	$C_{14}H_{11}N_3O_2SSe$	C	46.15	46.22
						H	3.02	3.11
IV*q*	4-Pyridyl	*p*-$CH_3C_6H_4SO_2$	70	142–145°	$C_{14}H_{11}N_3O_2SSe$	C	46.15	46.29
						H	3.02	3.13
V*a*	$C_6H_5SO_2CH_2$	H	26.5	147–151°	$C_9H_8N_2O_2SSe$	C	37.63	37.71
						H	2.78	2.66
V*b*	*p*-$CH_3C_6H_4SO_2CH_2$	H	44	148–150°	$C_{10}H_{10}N_2O_2SSe$	C	39.86	40.07
						H	3.32	3.28
V*c*	*p*-$CH_3C_6H_4SO_2CH(CH_3)$	H	58	137–139°	$C_{11}H_{12}N_2O_2SSe$	C	40.72	40.88
						H	2.48	2.53

diameter were immersed in the solution and placed on an inoculated assay medium surface[1].

The compounds were also tested against *Candida albicans* (ATCC 10231), *Aspergillus niger* (ATCC 16404), and *Penicillium notatum*[2]. Nystatin[3] was used as the control. Compounds were dissolved in dimethylformamide and diluted with hot culture medium (BBL Sabouraud dextrose agar medium). Concentrations of 10 and 25 mg of each compound/ml were used.

The antibacterial and antifungal activities are reported in Tables II and III, respectively. Most of the compounds tested were as active as the control compounds.

EXPERIMENTAL[4]

5-*p*-Toluenesulfonyl-1,2,3-selenadiazole (IV*a*)—α-*p*-Toluenesulfonyl acetaldehyde semicarbazone, 5.1 g (0.02 mole), was dissolved in 25 ml of boiling acetic acid. To the hot solution, 2 g (0.02 mole) of selenium dioxide was added; then the reaction mixture was stirred and gently heated until gas evolution ceased. The dark-brown mixture was heated with charcoal, filtered, and diluted with water. The precipitate was recrystallized from aqueous ethanol to give 3.22 g (58%) of cream needles, mp 129–131°; mass spectra: *m/e* 287 (M^+), 195 M − (SO_2, N_2), and 180 M − (Se, N_2); NMR (deuteriochloroform): δ 2.53 (s, 3H, CH_3), 7.3–8.0 (q, 4H, C_6H_4), and 8.9 (s, 1H, CH) ppm.

All 4-aryl-1,2,3-selenadiazoles reported in Table I were prepared similarly (Schemes I–III).

4-Phenylsulfonylmethyl-1,2,3-selenadiazole (V*a*)—Acetonylphenylsulfone semicarbazone, 5.1 g (0.02 mole), was dissolved in 25 ml of boiling acetic acid. To the hot solution, 2 g (0.02 mole) of selenium dioxide was added; then the reaction mixture was stirred until the vigorous reaction ceased.

The mixture was gently refluxed for 1 hr to complete the reaction. Charcoal was added, and the solution was filtered hot. To the filtrate, 15 ml of acetone was added; the mixture was then allowed to stand overnight at room temperature. The precipitate was filtered, and the mother liquor was worked up separately to afford IV*b*. The precipitate was recrystal-

Table II—Antibacterial Activity[a]

Compound	Average Inhibition Zone Diameter, mm			
	B. subtilis	*S. lutea*	*Staph. aureus*	*E. coli*
IV*a*	8	12	16	7
IV*b*	–	8	–	–
IV*c*	9	12	8	16
IV*d*	12	12	20	–
IV*e*	15	13	19	–
IV*g*	10	10	10	10
IV*h*	15	10	14	15
IV*j*	12	11	12	16
IV*k*	10	15	15	16
IV*l*	13	14	20	–
IV*m*	22	23	23	–
IV*o*	13	15	20	–
IV*p*	7	8	11	–
V*a*	10	8	10	7
V*b*	–	–	–	8
V*c*	8	8	–	–
Nitrofurazone	17	18	17	17

[a] – = inactive.

[1] AAM antibiotic assay medium, "The British Pharmacopoeia," 1968.

[2] This microorganism was obtained from the Department of Parasitology, Public Health Institute, Tehran, Iran.

[3] Mycostatin lot 2090a, potency 4858 U/mg, Squibb.

[4] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. Mass spectra were recorded on a Varian Matt 311 instrument. IR spectra were recorded with a Leitz model III instrument, and NMR spectra were recorded with a Varian T60A instrument. Aldehydes, ketones, and their semicarbazones were prepared by known methods.

Table III—Antifungal Activity [a]

Compound	*C. albicans*		*P. notatum*		*A. niger*	
	10 μg/ml	25 μg/ml	10 μg/ml	25 μg/ml	10 μg/ml	25 μg/ml
IV*a*	+	+	+	+	+	+
IV*b*	−	−	−	−	−	−
IV*c*	+	+	+	+	+	+
IV*d*	+	+	+	+	+	+
IV*e*	−	+	+	+	+	+
IV*g*	−	−	−	−	−	−
IV*h*	−	−	−	−	+	+
IV*j*	−	−	−	−	−	−
IV*k*	−	−	−	−	−	−
IV*l*	+	+	+	+	+	+
IV*m*	−	−	+	+	+	+
IV*o*	−	+	+	+	+	+
IV*p*	−	−	+	+	+	+
V*a*	+	+	+	+	+	+
V*b*	−	−	−	−	−	−
V*c*	−	−	−	−	−	−
Nystatin	+	+	+	+	+	+

[a] − = inactive.

lized from hot acetone to give 1.5 g (26.5%) of white needles, mp 147–151°; mass spectra: *m/e* 287 (M^+), 233 M − (SO_2), 195 M − (SO_2, N_2), and 180 M − (Se, N_2); NMR (deuteriochloroform): δ 5.1 (s, 2H, CH_2), 7.4–7.7 (m, 5H, C_6H_5), and 9.45 (s, 1H, CH) ppm.

4-Methyl-5-phenylsulfonyl-1,2,3-selenadiazole (IV*b*)—The mother liquor from the preparation of V*a* was diluted with an excess of water. After refrigeration, it gave 3.5 g of brownish crystals, which were recrystallized from diluted acetone to give 3.1 g (54%) of IV*b*, mp 76–78°; mass spectra: *m/e* 278 (M^+), 195 M − (SO_2,N_2) and 180 M − (Se, N_2); NMR (deuteriochloroform): δ 2.88 (s, 3H, CH_3) and 7.3–8.1 (m, 5H, C_6H_5) ppm.

The isomeric compounds V*b* and IV*c* were prepared similarly. The ratio of V*b* to IV*c* was 44:56 (Table I).

Photolysis of Disubstituted-1,2,3-selenadiazoles—p-*Toluenesulfonylpropyne* (*VI*a)—4-Methyl-5-*p*-toluenesulfonyl-1,2,3-selenadiazole (IV*c*), 3 g (0.01 mole), in 90 ml of dry benzene was photolyzed during 6 hr using a 100-w high-pressure mercury lamp. The solution was filtered and evaporated at low pressure, and the crystalline residue was recrystallized from petroleum ether to give 0.81 g (42%) of white crystals, mp 96–97° [lit. (7) mp 98–99°]; IR: λ_{max} 2200 (C≡C), 1328, 1291, 1152, 1087, 818, and 706 cm^{-1}.

Anal.—Calc. for $C_{10}H_{10}O_2S$: C, 61.85; H, 5.15. Found: C, 61.99; H, 5.17.

p-*Toluenesulfonylacetylene* (*VI*b)—Photolysis of IV*e* as indicated for the preparation of VI*a* afforded 64% of the desired compound, mp (petroleum ether) 79–81° [lit. (8) mp 80–81°]; IR: 2109 (C≡C) cm^{-1}.

Anal.—Calc. for $C_{15}H_{12}O_2S$: C, 70.31; H, 4.53. Found C, 70.22; H, 4.40.

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Effect of Dissolved Oxygen Levels on Oxidative Degradation of Pyrogallol

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Received September 16, 1977, from the *School of Pharmacy, University of Wyoming, Laramie, WY 82071.* Accepted for publication January 10, 1978.

Abstract □ Pyrogallol decomposition in aqueous systems with various dissolved oxygen levels was studied. The reduced dissolved oxygen levels were produced by deaeration *via* gas permeation. Dissolved oxygen levels were determined using a dropping mercury electrode polarograph. Degradation rates, T_{90}, and relative protection indexes are discussed. Even at dissolved oxygen levels of less than 0.05 ppm, some decomposition of pyrogallol occurred, indicating nonoxidative pathways or the necessity of total removal of dissolved oxygen to afford complete protection. Apparently, reducing the level of dissolved oxygen is a viable alternative to stabilization of aqueous pyrogallol solutions, since the T_{90} was increased from 1.9 days in water with dissolved oxygen levels of 9.05 ppm to 114.4 days in water with dissolved oxygen levels of less than 0.05 ppm.

Keyphrases □ Pyrogallol—oxidative degradation in aqueous systems, effect of dissolved oxygen levels □ Degradation, oxidative—pyrogallol in aqueous systems, effect of dissolved oxygen levels □ Oxidative degradation—pyrogallol in aqueous systems, effect of dissolved oxygen levels □ Antibacterials, topical—pyrogallol, oxidative degradation in aqueous systems, effect of dissolved oxygen levels

An important factor in drug stabilization is reduction of oxidative degradation. The sensitivity of several drugs to oxidative degradation was studied previously (1–5), and several techniques were used to inhibit this degradative pathway (6). Autoxidation of pharmaceuticals was described as a process mediated by free radicals: initiation, propagation *via* free radicals, and termination of the reaction to form inactive products (7).

If molecular oxygen, necessary for the propagation step, were substantially reduced, oxidative processes might be significantly reduced or eliminated. Therefore, the propagation step assumes major importance in free radical-

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