Selenium Heterocycles VIII: Synthesis and Antibacterial Activity of Selenosemicarbazide and 1,3,4-Selenadiazolylcarbamic Acid Esters

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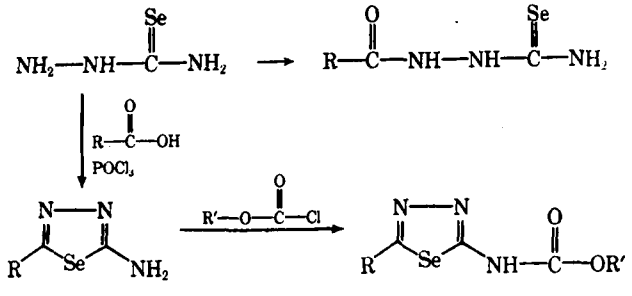
Abstract □ The antibacterial activity of selenosemicarbazide and its acyl derivatives was compared with the activity of their sulfur and oxygen analogs. A series of 1,3,4-selenadiazolylcarbamic acid esters was also prepared and tested. Some of these compounds showed significant antibacterial activity.

Keyphrases □ Selenosemicarbazide and acyl derivatives—synthesis, antibacterial activity compared with sulfur and oxygen analogs □ 1,3,4-Selenadiazolylcarbamic acid esters—synthesis, antibacterial activity □ Antibacterial activity—synthesis of selenosemicarbazide derivatives and 1,3,4-selenadiazolylcarbamic acid esters

Recently, we reported (1, 2) that 1,3,4-thiodiazolylcarbamic acid esters have potent antibacterial and antiviral activity. Bhamaria *et al.* (3) reported that 1-acyl 4-alkyl (or aryl) thiosemicarbazides have no significant antibacterial activity against *Escherichia coli* and *Salmonella typhosa* and very limited activity against *Staphylococcus aureus*, but the majority of the compounds tested were active against *Mycobacterium tuberculosis*. Bednarz (4) reported that selenosemicarbazides of aldehydes were active against *M. tuberculosis*, *S. aureus*, *Bacillus subtilis*, and *E. coli*. Therefore, the comparative study of antibacterial activity of a series of selenium compounds and their analogs was of special interest.



Scheme I

EXPERIMENTAL[1]

The desired compounds were prepared according to Scheme I. The physical data of these compounds are summarized in Tables I and II.

All compounds listed in Table III were tested against *B. subtilis* (NCTC 3610), *S. aureus* (ATCC 6538), *Klebsiella pneumoniae* (ATCC 10031), and *Sarcina lutea* (ATCC 9341).

The compounds were dissolved in sterile distilled water and diluted to a 0.5% concentration. Standard paper disks of 6 mm. diameter were immersed in solution and were placed on inoculated assay medium surface[2]. None of the 1-acyl semicarbazides or 1-acyl thiosemicarbazides and their derivatives showed significant activity (Table III).

All compounds listed in Table II were tested against *S. aureus* (ATCC 6538p) and *K. pneumoniae* (ATCC 10031) at different concentrations in liquid medium[3]. Compounds 6, 7, and 12 at the concentration of 0.6 mg./ml. inhibited the growth of these organisms. No significant inhibition was observed with the other compounds up to the concentration of 2.5 mg./ml.

Selenosemicarbazide was prepared according to the literature (5).

1-Formylselenosemicarbazide (Compound 1)—Selenosemicarbazide (2.76 g., 0.02 mole) and 10 ml. of 99–100% formic acid were refluxed for 20 min. The reaction mixture was filtered hot, allowed to crystallize at room temperature, and recrystallized from water.

1-Propionylselenosemicarbazide (Compound 2)—This compound was prepared from propionic acid and selenosemicarbazide similar to 1-formylselenosemicarbazide.

Other 1-acyl selenosemicarbazides were prepared by the method reported previously (6).

1-Benzoylselenosemicarbazide (Compound 3)—Selenosemicarbazide (2.76 g., 0.02 mole) was dissolved in 40 ml. of 4% sodium hydroxide and, while stirring at ice bath temperature, benzoyl chloride (2.8 g., 0.02 mole) was added dropwise. After standing at room temperature for 1 hr., charcoal was added to the reaction mixture, which was then filtered and acidified with 10% hydrochloric acid and the precipitate was recrystallized from ethanol–water.

***N*-(5-Trifluoromethyl-1,3,4-selenadiazol-2-yl)carbamic Acid Ester (Compound 12)**—2-Amino-5-trifluoromethyl-1,3,4-selenadiazole (6)

Table I—1-Acyl Selenosemicarbazides RCONHNHCSeNH₂

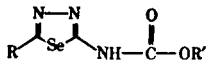
Compound	R	Melting Point	Yield, %	Crystallization Solvent	Formula	Analysis, % Calc.	Found
1	H	172°	50	Water	$C_2H_5N_3OSe$	C 14.45	14.33
						H 3.01	2.96
2	C_2H_5	182°	40	Ethanol	$C_4H_9N_3OSe$	C 24.72	24.89
						H 4.63	4.55
3	C_6H_5	210–214°	76	Ethanol–water	$C_8H_9N_3OSe$	C 39.66	39.39
						H 3.70	3.80
4	*p*-FC_6H_4	198–200°	72	Water	$C_8H_8FN_3OSe$	C 36.92	37.02
						H 3.07	2.99

[1] Melting points were taken on a Kofler hot stage microscope and are uncorrected. Their spectra were recorded using a Leitz spectrograph. NMR spectra were recorded on a Varian A60A instrument.

[2] Antibiotic assay medium, British Pharmacopoeia, 1968.

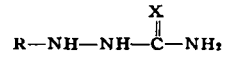
[3] Antibiotic assay medium without agar, British Pharmacopoeia, 1968.

Table II—5-Substituted-1,3,4-selenadiazol-2-yl-carbamic Acid Esters



Compound	R	R′	Melting Point	Yield, %	Crystallization Solvent	Formula	Analysis, % Calc.	Found
5	CH_3	CH_3	170°	63	Water	$C_5H_7N_3O_2Se$	C 27.14	27.21
							H 3.16	3.09
6	CH_3	n-C_4H_9	165°	69	Water	$C_8H_{13}N_3O_2Se$	C 36.50	36.29
							H 4.92	5.01
7	CH_3	iso-C_4H_9	155°	77	Water	$C_8H_{13}N_3O_2Se$	C 36.50	36.66
							H 4.92	4.99
8	C_2H_5	CH_3	147°	82	Water	$C_6H_9N_3O_2Se$	C 30.63	30.77
							H 3.82	3.78
9	C_2H_5	C_2H_5	119°	80	Water	$C_7H_{11}N_3O_2Se$	C 33.73	33.71
							H 4.41	4.49
10	C_6H_5	CH_3	148°	53	Water	$C_{10}H_9N_3O_2Se$	C 42.40	42.43
							H 3.18	3.17
11	C_6H_5	C_2H_5	132°	66	Water	$C_{11}H_{11}N_3O_2Se$	C 44.44	44.26
							H 3.70	3.66
12	CF_3	C_2H_5	204°	77	Water	$C_6H_6F_3N_3O_2Se$	C 24.91	25.06
							H 2.07	2.11

Table III—Average Zone Size, mm.



R	X	*B. subtilis*	*K. pneumoniae*	*S. aureus*	*Sar. lutea*
H	Se	23	48	30	40
HCO	S	—	—	—	—
HCO	Se	20	24	19	45
CH_3CO	S	—	—	—	—
CH_3CO	Se	21	35	29	32
C_6H_5CO	S	—	—	—	—
C_6H_5CO	Se	14	34	23	36
C_6H_5CO	O	—	—	—	—
C_6H_5CO	S	—	—	—	—
C_6H_5CO	Se	19	39	26	41
p-FC_6H_4CO	Se	19	38	27	42

(0.55 g., 0.025 mole) and chloroformic acid ethyl ester (0.28 g., 0.026 mole) in 18 ml. chloroform were refluxed for 2 hr. After removing the solvent, the residue was crystallized from water to give 0.55 g. (77%) of Compound 12.

All other compounds were prepared similarly (Table II).

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