acidic carboxylic group of aspirin may be achieved by making derivatives similar to Compound I. One possible advantage of a compound such as I is that the mucous membranes of the stomach are in contact with a neutral molecule. As I dissolves, however, it will rapidly hydrolyze, generating aspirin in solution. The mechanism of hydrolysis of I was shown to proceed by a classical S_N1-type reaction.

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Selenium Heterocycles X: Synthesis and Antibacterial Activity of Pyridyl-1,2,3-thiadiazoles and Pyridyl-1,2,3-selenadiazoles

I. LALEZARI[x], A. SHAFIEE, and S. YAZDANY

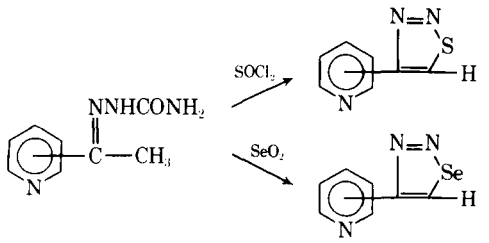
Abstract □ Three isomeric 4-pyridyl-1,2,3-selenadiazoles and their corresponding diselenafulvines were prepared. 4-(3-Pyridyl)-1,2,3-thiadiazole and its dithiafulvene were also synthesized. The hydrochloride salts of all compounds prepared showed significant antibacterial activity.

Keyphrases □ Selenium heterocycles—synthesis and antibacterial activity of pyridyl-1,2,3-thiadiazoles and pyridyl-1,2,3-selenadiazoles □ Pyridyl-1,2,3-thiadiazoles and selenadiazoles—synthesized and screened as antibacterial agents □ Selenadiazoles, pyridyl-1,2,3—synthesized and screened as antibacterial agents □ Antibacterial agents, potential—synthesis and screening of pyridyl-1,2,3-thiadiazoles and pyridyl-1,2,3-selenadiazoles

Recently, the synthesis of 1,2,3-selenadiazoles by selenium dioxide oxidation of aldehyde or ketone semicarbazones having an α-methyl or methylene group was reported (1–4). It was also shown that 1,2,3-selenadiazoles and base afforded 1,4-diselenafulvenes (5).

DISCUSSION

In the present work, the three isomeric 4-pyridyl-1,2,3-selenadiazoles were prepared. Also, 4-(3-pyridyl)-1,2,3-thiadiazole was prepared in high yield by reaction of thionyl chloride and 3-acetylpyridine semicarbazone (Scheme I). All thia- and selenadiazoles prepared (Tables I and II) were converted to the corresponding dithia- and diselenafulvenes by reaction with potassium hydroxide in ethanol (Scheme II).



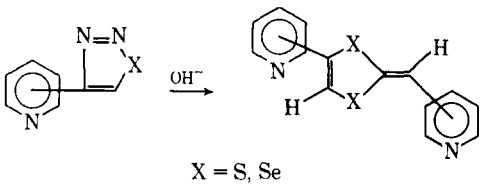
Scheme I

Some of the 1,3,4-thiadiazole derivatives have shown antibacterial and antiviral activities (6, 7). Also, 1,2,3-selenadiazole and some of its derivatives were found to have significant antibacterial activity (5). In the search for new potent antibacterial agents, it was of interest to study the antibacterial activity of the pyridyl thia- and selenadiazoles closely related to these compounds. All compounds (Tables I and II) were tested against *Bacillus subtilis* NCTC 3610, *Staphylococcus aureus* ATCC 6538, *Klebsiella pneumoniae* ATCC 10031, and *Sarcina lutea* ATCC 9341. Nitrofurazone was used as a control. Standard paper disks of 6 mm diameter were immersed in solution and placed on inoculated assay medium surface[1].

The antibacterial activity of all compounds that were dissolved in acetone at the concentration 0.5% were insignificant. However, the hydrochloride salts (prepared by dissolving the base in dilute hydrochloric acid and drying at room temperature in the dark) at a concentration of 0.5% in distilled water (and nitrofurazone dissolved in dimethylformamide at the same concentration) were active (Table III).

EXPERIMENTAL[2]

4-(2-Pyridyl)-1,2,3-selenadiazole (I)—2-Acetylpyridine semicarbazone (4.4 g, 0.025 mole) was dissolved in 50 ml of boiling

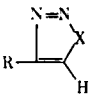


Scheme II

[1] Antibiotic Assay Medium; British Pharmacopoeia, 1968.

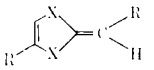
[2] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. The IR spectra were recorded using a Leitz spectrograph. UV spectra were obtained with a Varian Techtron 635 instrument. The mass spectra were recorded on a Varian Mat 111 instrument.

Table I—1,2,3-Thia- and Selenadiazoles



Compound	R	X	Melting Point	Yield, %	Formula	Analysis, % Calc.	Found
I	2-Pyridyl	Se	79–81°	65	$C_7H_5N_3Se$	C 39.81	39.99
						H 2.37	2.39
II	3-Pyridyl	Se	85°	52	$C_7H_5N_3Se$	C 39.81	39.86
						H 2.37	2.29
III	4-Pyridyl	Se	132°	48	$C_7H_5N_3Se$	C 39.81	39.82
						H 2.37	2.40
IV	3-Pyridyl	S	88–90°	82	$C_7H_5N_3S$	C 51.53	51.44
						H 3.07	3.06

Table II—*trans*-Dithiafulvenes and *trans*-Diselenafulvenes



Compound	R	X	Melting Point	Yield, %	Formula	Analysis, % Calc.	Found
V	2-Pyridyl	Se	258–260°	85	$C_{14}H_{10}N_2Se_2$	C 45.90	45.92
						H 2.73	2.80
VI	3-Pyridyl	Se	170–175°[a]	92	$C_{14}H_{10}N_2Se_2$	C 45.90	46.01
						H 2.73	2.72
VII	4-Pyridyl	Se	250°[b]	86	$C_{14}H_{10}N_2Se_2$	C 45.90	45.99
						H 2.73	2.70
VIII	3-Pyridyl	S	188–190°	83	$C_{14}H_{10}N_2S_2$	C 62.22	62.26
						H 3.70	3.78

[a] *cis*-Isomer, mp 130–132°. [b] *cis*-Isomer, mp 183–185°.

acetic acid. To the hot solution, 2.75 g (0.025 mole) of selenium dioxide was added and the reaction mixture was stirred until the vigorous reaction ceased. Heat was applied for 0.5 hr to complete the reaction. Charcoal was added and the solution was filtered hot, diluted with 250 ml of water, and extracted with 50 ml of chloroform. The organic layer separated and was washed with 10% sodium bicarbonate solution and then with water. After evaporation of the solvent, the crystalline residue was recrystallized from benzene containing 25% petroleum ether to give 3.3 g of I (65%), mp 79–81°; molecular weight (by mass spectroscopy): 211; UV: λ_{max} 269 and 306 nm; IR: ν_{max} 3330, 3130, 1587, 1493, 1417, 1344, 1293, 1235, 1055, 1017, 960, 916, 818, 799, 777, 740, and 727 cm^{-1}.

4-(3-Pyridyl)-1,2,3-selenadiazole and 4-(4-pyridyl)-1,2,3-selenadiazole were prepared similarly.

4-(3-Pyridyl)-1,2,3-thiadiazole (IV)—3-Acetylpyridine semicarbazone (5.34 g, 0.03 mole) was added portionwise to 15 ml of thionyl chloride at ice bath temperature and kept 0.5 hr at room temperature. Chloroform, 50 ml, was added and the mixture was decomposed with ice-cold concentrated sodium carbonate solution. The organic layer was washed with water and dried with anhydrous sodium sulfate. After evaporation of the solvent, the crystalline mass was recrystallized from aqueous ethanol to give 4 g (82%) of IV, mp 88–90°; molecular weight (by mass spectroscopy): 163.

2,ω-Di(2-pyridyl)-1,4-diselenafulvene (V)—4-(2-Pyridyl)-1,2,3-selenadiazole (1.0 g, 5 mmoles) was dissolved in 20 ml of 95% ethanol and a pellet of potassium hydroxide was added. After gas evolution ceased, water was added and the crystals were filtered, washed with water, and recrystallized from ethanol to give 0.77 g (85%) of V, mp 258–260°; molecular weight (by mass spectroscopy): 366; UV: λ_{max} 245 and 385 nm; IR: ν_{max} 3305, 1582, 1518, 1455, 1400, 1380, 1215, 1145, 1052, 990, 908, 880, 823, 780, and 743 cm^{-1}.

Table III—Antibacterial Activity[a]

Compound[b]	Average Inhibition Zone Diameter, mm *B. subtilis*	*K. pneumoniae*	*Staph. aureus*	*S. lutea*
I	14	15*	8*	14
II	10	15	10*	8
III	10	18	16	10
IV	12	–	–	12
V	15	–	14	25
VI	16	15	17	18
VII	14	15	17	13
VIII	14	8	18*	17
Nitrofurazone	18	21	23	20

[a] – = inactive; * = inhibition zones were hazy. [b] As the hydrochloride.

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