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SELENIUM HETEROCYCLES XXXVIII [1]. SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF 2-ARYLSELENAZOLES

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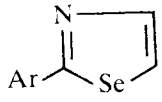
Abstract

Starting from substituted selenobenzamides (2) a series of 2-arylselenazoles (3-7) were prepared. The antibacterial activity of compounds **3-7** against a number of microorganisms were determined. Some of these compounds showed significant antibacterial activity.

Introduction

In continuation of the study on the chemistry of selenium heterocyclic compounds [2-8] and as a part of the program designed to expand the chemistry of thiazole and selenazole heterocycles [9-10] it became necessary to synthesize 2-arylselenazole (3) and its derivatives for biological evaluation.



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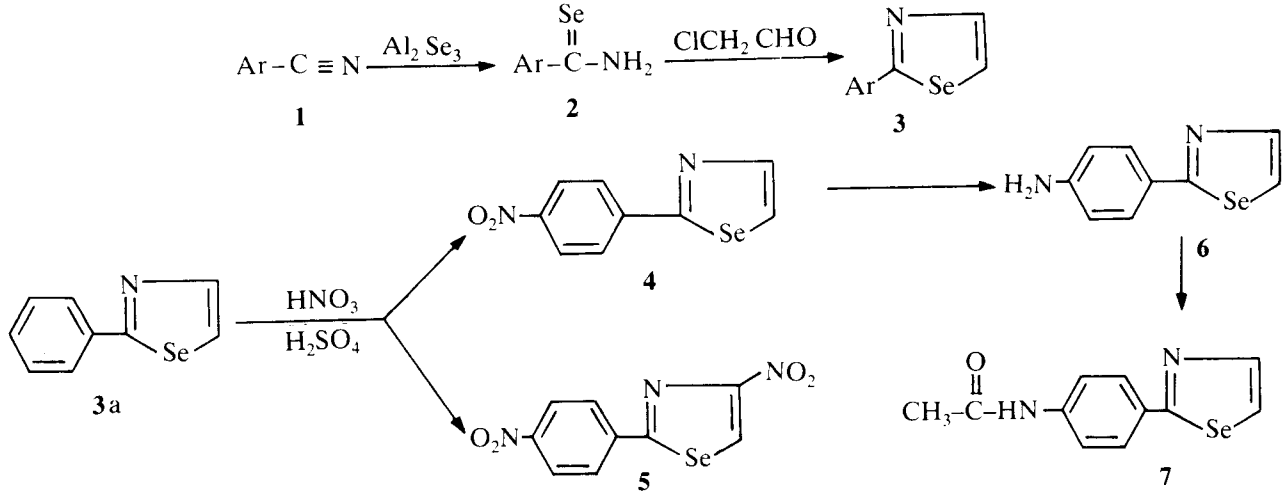
Results and Discussion

2-Arylselenazole (**3**) could be readily prepared through the reaction of substituted selenobenzamide (**2**) [11] with α-chloroacetaldehyde in dioxane (Scheme 1).

The NMR spectra of 2-arylselenazoles were in agreement with the suggested structure (Table 1).

The NMR of compound **3** was quite characteristic. H_4 and H_5 of the selenazole ring appeared at 7.96-7.73 ppm mostly as a singlet. Only, in the case of o-

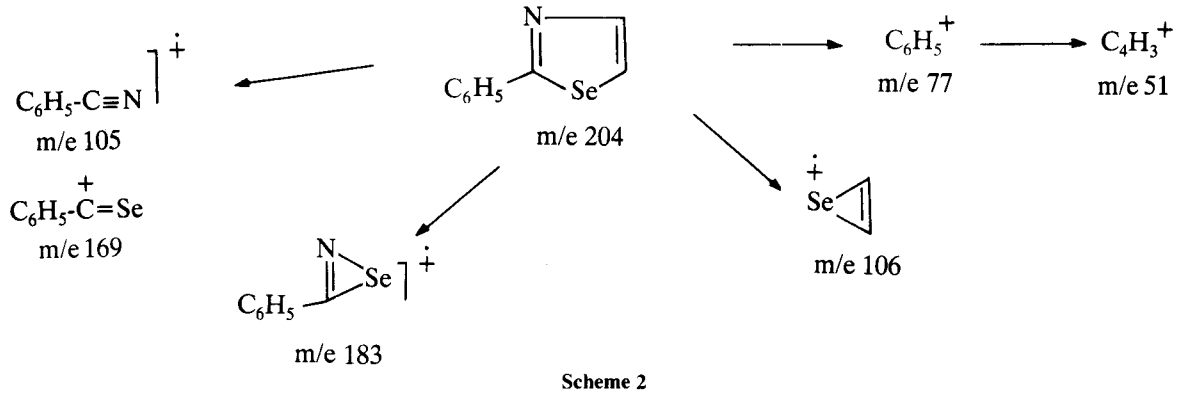


Scheme 1

Table 1. Physical Constants of 2-Arylselenazoles.

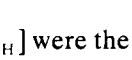
Compound[d] NO.	Ar	B.P. (8 mm Hg) or m.p. °C	Yield%	λ_{max} (nm, logϵ)	NMR (δ $CDCl_3$)
3a	C_6H_5	140-142 (18 mm Hg)	45	290(3.32)	8.0-7. 53 (m, 2H, aromatic), 7.76 (s, 2H, $H_{4,5}$), 7.50-7.03 (m, 3H, aromatic).
3b	p-BrC_6H_4-	38-40[a]	50	306(4.2)	7.83 (s, 2H, $H_{4,5}$), 7.76 (d, 2H, aromatic), 7.53 (d, 2H, aromatic).
3c	oClC_6H_4-	150-153	26	302(3.79)	8.28 (q, lH, aromatic), 7.93 (2d, 2H, $H_{4,5}$, $J_{4,5}$ =4 7.26 (m, 3H, aromatic).
3d	p-ClC_6H_4-	148-150	20	304(4.29)	7.76 (m, 4H, aromatic), 7.36 (m, 2H, aromatic).
3e	o -$CH_3C_6H_4$-	150-152	47	290(3.6)	7.96 (s, 2H, $H_{4,5}$), 7.60 (m, lH, aromatic), 7.23 (m, 3H, aromatic), 2.56 (s, 3H, CH_3).
3f	m-$CH_3C_6H_4$-	146-148	35	300(3.9)	7.73 (s, 2H, $H_{4,5}$), 7.66 (m, 2H, aromatic), 7.13(m, 2H, aromatic), 2.30 (s, 3H, CH_3)
3g	p-$CH_3C_6H_4$-	148-150	50	292(3.63)	7.76 (s, 2H, $H_{4,5}$), 7.73 (d, 2H, aromatic), 7.16 (d, 2H, aromatic), 2.30 (s, 3H, CH_3).
3h	p-$CH_3OC_6H_4$-	150-151	35	304(4.4)	7.81 (s, 2H, $H_{4,5}$), 7.70 (d, 2H, aromatic), 6.80 (d, 2H, aromatic), 3.73 (s, 3H, CH_3O).
4	p-$NO_2C_6H_4$-	128-130[b]	35	334(4.18)	8.36 (d, 2H, aromatic), 8.13 (2d, 2H, aromatic), 8.11 (2d, 2H, $H_{4,5}$).
5	p-$NO_4C_6H_4$-4-nitro-	178-180[b]	25	334(4.9)	8.70 (s, lH, H_5), 8.40 (d, 2H, aromatic), 8.13 (d, 2H, aromatic)
6	2-p-$NH_2C_6H_4$-	110-111[c]	35	334(4.55)	7.76 (s, 2H, $H_{4,5}$), 7.46 (d, 2H, aromatic), 6.50 (d, 2H, aromatic).
7	2-p-$CH_3CONHC_6H_4$	130-132[b]	30	307(4.44)	7.90-7.23 (m, 6H, aromatic), 2.16 (s, 3H, CH_3)

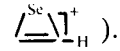
a) This compound was crystallized from ether- petroleum ether. b) This compound was crystallized from ether. c) This compound was crystallized from water. d) Elemental analyses gave satisfactory results.



Scheme 2

chlorophenylselenazole (3c) and p-nitrophenylselenazole (4) these hydrogens appeared as two doublets ($J_{4,5}$=4Hz). This observation was different from the one reported for 2-arylthiazole [12]. The mass spectra fragmentation pattern was also in agreement with the suggested structure, which for 2-phenylselenazole is summarized in Scheme 2.

For 2-arylselenazole, the nitrile (Ar-C≡N) and ion m/e 106 [] were the most abundant peaks. The fragmentation pattern was similar to 2-phenylthiazole reported previously [13].

Nitration of 2-phenylselenazole with a mixture of nitric acid and sulfuric acid afforded two compounds which was separated by preparative tlc. The fast moving fraction was 2-**p**-nitrophenylselenazole (4). The slow moving fraction was 2-**p**-nitrophenyl-4-nitroselenazole (**5**). The NMR spectrum and mass spectrum fragmentation pattern were in agreement with the suggested structures. The NMR spectrum of compound **5** had a singlet at 8.70 (H_5), integrating for one proton, and two doublets at 8.4 and 8.13 ppm integrating each for two protons. In the mass spectrum the most abundant ion was at m/e 105 (). This demonstrated that one of the hydrogen at C_4 or C_5 of the selenazole ring is substituted by a nitro group. The other ions were also in agreement with the suggested structure (see Experimental Section).

Reduction of compound **4** afforded 2-**p**-aminophenylselenazole (**6**). Reaction of compound 6 with acetic anhydride gave 2-**p**-acetamidophenylselenazole (**7**).

Previously, we reported that 1,3,4-selenadiazolylcarbamic acid esters have significant antibacterial activity [14]. In the present work, antibacterial activity of compounds **3** to **7** were determined and summarized in Tables 2 and 3.

Experimental Section

General remarks. Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The IR spectra were obtained using a Perkin-Elmer Model 267 spectrograph (potasium bromide disks). The NMR spectra were recorded on a Varian T-60 spectrometer and chemical shifts (δ) are in ppm relative to internal tetramethylsilane. Mass spectra were run on a

Table 2. Average zone size (mm) for 0.1% concentration of the compounds.

Compounds	*B. Subtilis*	*Sar. Lutea*	*S. aureus*
3a	16	14	15
3b	-	-	-
3c	-	-	-
3d	-	-	-
3e	24.5	35	39
3f	15	15	20.4
3g	-	-	-
3h	-	-	-
4	-	-	-
5	20.5	15	14.5
6	-	14	-
2-**p**-aminophenylthiazole[15]	-	-	-
2-**p**-acetamidophenylthiazole[16]	-	-	-
Nitrofurantoin	25.8	14	23

Table 3. Average zone size (mm) for 0.025% concentration of the compounds.

Compound	*B. Subtilis*	*Sar. lutea*	*S. aureus*
3e	22.8	16.4	31.4
3f	16	-	-
5	20.8	-	15.2
Nitrofurantoin	21.2	-	18

Varian Model MAT MS-311 spectrometer at 70 ev.

2- Phenylselenazole (**3a**).

To a stirred solution of selenobenzamide (**2a**, 3.42 g, 0.02 mole) in dioxane (100 ml) a 50% aquous solution of α-chloroacetaldehyde (3.74 ml) was added. The mixture was heated at 60°C for 3 hrs and 20 ml of dioxane was removed at reduced pressure. The residue was heated at 100°C for 2 hrs and the solvent was evaporated. Water (10 ml) was added to the residue. It was made alkaline with a saturated sodium bicarbonate solution and extracted with chloroform. The extract was dried with soldium sulfate, filtered and evaporated. The residue was distilled under reduced pressure to give 1.87 g (45%) of **3** a; b.p. 140-142 (8 mm Hg); IR: 3120, 3060 cm^{-1} (H-C_4 and H-C_5 of selenazole); NMR (deuteriochloroform): 8.0-7.53 (m, 2H, aromatic), 7.76 (s, 2H, $H_{4,5}$) and 7.50-7.03 ppm (m, 3H, aromatic); ms: m/e (%) 209 (M^+, 97), 207(64), 205(25), 106 [ , 100], 104(97), 77 (86), 76 (54), 51 (75), 50 (51), 39 (26).

Anal Calcd. for C_9H_7NSe: C, 51.92; H, 3.37; N, 6.73. Found: C, 52.05; H, 3.49; N, 6.61.

Other 2-arylselenazoles were prepared similary (see Table 1).

*2-***p**- *Nitrophenylselenazole* (**4**) and 2-**p**- *Nitrophenyl-4-nitroselenazole* (**5**).

To a stirred solution of **3a** (1.04 g, 0.005 mole) in concentrated sulfuric acid (4 ml), at 0°C, conc. sulfuric acid (2.4 ml) and fuming nitric acid (1.6 ml) was added. The mixture was let to stand at -5° to 0° for 1/2 hr and poured into ice-water. The precipitate was filtered and purified by preparative tlc on silica gel using chloroform as the eluent. The fast moving fraction was crystallized from methanol to give 0.44 g (35%) of **4**, m.p. 178-180°C; IR: 3125, 3080 (H_{C-4} and H_{C-5} of selenazole), 1520, 1340 cm^{-1} (NO_2); NMR (deuteriochloroform): 8.36 (d, 2H, aromatic), 8.13 (d, 2H, aromatic) and 8.11 ppm (2d, 2H, $H_{4,5}$); ms: m/e (%) 254 (M^+, 74), 256 (37), 224 (41), 208 (7), 182 (13), 128 (8), 106 (100), 104 (97), 76 (56), 75 (56) and 50 (46).

Anal. Calcd. for $C_9H_6N_2O_2Se$: C, 42.69; H, 2.37; N, 11.6. Found: C, 42.71; H, 2.49; N, 11.45.

The slow moving fraction was crystallized from methanol to give 0.37 g (25%) of 5; m.p. 178-180°C; IR: 3100 (H-C_5 selenazole), 1520, 1340 cm^{-1}(NO_2); NMR (deuteriochloroform): 8.70 (s, 1H, H_5), 8.40 (d, 2H, aromatic) and 8.13 ppm (d, 2H, aromatic); ms: m/e (%) 299 (M^+, 42), 297 (20), 253 (M^+-NO_2, 75), 251 (38), 207 (M^+-$2NO_2$, 6), 105 [ , 100], 103 (86), 75 (23), 50 (17), and 30 (10).

Anal. Calcd. for $C_9H_5N_3O_4Se$: C, 36. 24; H, 1.68; N, 14.09. Found: C, 36.37; H, 1.79; N, 14.21

2-p-Aminophenylselenazole (**6**).

To a stirring solution of ammonium chloride (0.2 g) in water (5 ml), compound 4 (506 mg, 2 mmoles) and iron powder (2 g) were added. The mixture was heated at 80°C for 2 hrs. After cooling, it was extracted with chloroform. The extract was dried with sodium sulfate, filtered and evaporated. The residue was crystallized from water to give 156 mg (35 %) of 6; m.p. 110-111°C; IR: 3450, 3300, 3195 (NH), 3100, 3075 (H-C_4 and H-$C_5$of selenazole), 1630 cm^{-1} (NH); NMR (deuteriochloroform): 7.76 (s, 2H, $H_{4,5}$), 7.46 (d, 2H, aromatic), and 6.50 ppm (d, 2H, aromatic); ms: m/e (%) 224 (M^+, 100), 222 (97), 198 (36), 196 (18), 118 (97), 106 (77), 104 (37), and 91 (21).

Anal. Calcd. for $C_9H_8N_2Se$: C, 48.43; H, 3.59; N, 12.56. Found: C, 48.31; H, 4.05; N, 12.39.

2-p-Acetamidophenylselenazole (**7**).

A solution of compound 6 (223 mg. lmmol) in acetic anhydride (3 ml) was refluxed for 10 minutes. The excess acetic anhydride was removed under reduced pressure. To the residue water (5 ml) was added. It was made alkaline with sodium bicarbonate solution and extracted with chloroform. The solvent was removed under reduced pressure and the residue was purified by tlc on silica gel using chloroform-methanol (95:5) as eluent to give 79.5 mg (30 %)of 7; m.p. 130-132°C (ether); IR: 3300 (NH), 3095, 3070 (H-C_4 and H-C_5 of selenazole), and 1670 cm^{-1}(CO); NMR (deuteriochloroform): 7.93-7.23 (m, 6H, aromatic) and 2.16 ppm (s, 3H, CH_3).

Anal. Calcd. for $C_{11}H_{10}N_2OSe$: C, 49.81; H, 3.77; N, 10.57. Found: C, 49.94; H, 3.63; N, 10.41.

Antibacterial Assay- All compounds listed in Table 1 were tested against *Pseudomonas aeruginosa* (ATCC 9027), *Escherichia coli* (ATCC 7839), *S. aureus* (ATCC 6538 p), *B. subtilis* (ATCC 6633) and *Sarcina lutea* (ATCC 9341).

The compounds were dissolved in acetone and diluted to a 0.1 % concentration with acetone. Standard paper disks of 12.7 mm diameter were immersed in solution and after drying were placed on an inoculated assay medium surface. Nitrofurantoin was used for comparison. These compounds have no significant antibacterial activity against *Pseudomonas aeroginosa*

and very limited activity against *Escherichia coli*. The antibacterial activity against other microorganisms are summarized in Table 2. Since compounds **3e**, **3f** and **5** showed significant antibacterial activities, they were also tested at 0.025% concentration. The result is summarized in Table **3**. Compounds 3e and **5** were the most active compounds.

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