Selenium Heterocycles. IV
Synthesis of 2-Amino-1,3,4-selenadiazoles and 2-Substituted-6-phenylimidazo[2,1-*b*]-1,3,4-selenadiazoles

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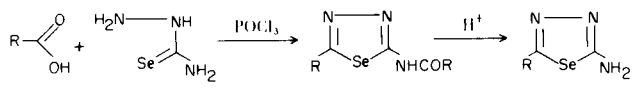
In continuation of our study on the chemistry of selenium heterocyclic compounds (1-3), we have prepared 2-amino-1,3,4-selenadiazoles (**4a-e**) and 2-substituted-6-phenylimidazo[2,1-*b*]-1,3,4-selenadiazoles (**7a-d**).

Recently, we reported that 1,3,4-thiadiazolylcarbamic acid esters have potent antiviral and antimicrobial activities (4,5); therefore, the study of the chemistry and possible pharmacological activity of 2-amino-1,3,4-selenadiazoles (**4a-e**) was of special interest.

It has been shown that the vacuum distillation of diacetyl hydrazine with phosphorus pentaselenide affords 2,5-dimethyl-1,3,4-selenadiazole (6). *N,N*-Dimethylformamide azine and hydrogen selenide gave 1,3,4-selenadiazole (7). Neither of these methods, however, seemed to be feasible for the synthesis of the desired compounds.

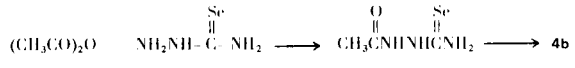
The general method for the synthesis of 2-amino-1,3,4-thiadiazoles (8) was modified and adopted for the synthesis of their selenium analogues. When a mixture of the appropriate carboxylic acid and selenosemicarbazide (**1**) was heated with an excess of phosphorus oxychloride and worked up carefully, high yields of 2-acylamino-5-substituted-1,3,4-selenadiazoles (**3**) were obtained which could be subsequently hydrolyzed to 2-amino-5-substituted-1,3,4-selenadiazoles (**4**) (Method A).



2 1 3 4

a: R = H d: R = CF_3
b: R = CH_3 e: R = C_6H_5
c: R = C_2H_5

To ascertain the structure of 2-amino-5-substituted-1,3,4-selenadiazoles (**4**), 2-amino-5-methyl-1,3,4-selenadiazole (**4b**) was synthesized by the acetyl chloride cyclization of 1-acetylselenosemicarbazide (**8**) which was prepared from acetic anhydride and selenosemicarbazide in chloroform (Method B).



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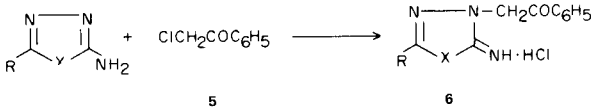
The nmr spectrum of 2-amino-1,3,4-selenadiazole (**4a**) was of particular interest. Recently, we reported (3) that the selenium isotope (^{77}Se) couples with the geminal proton in 4-substituted-1,2,3-selenadiazoles. The selenium splitting constant was found to be 40 cps. The splitting constant in **4a** was found to be 55 cps.

The physical data of 2-amino-5-substituted-1,3,4-selenadiazols (**4**) are listed in Table I.

The reaction of 2-amino-1,3,4-selenadiazoles (**4**) with 2-chloroacetophenone led to the formation of compounds (**6**), which were cyclized to 2-substituted-6-phenylimidazo-[2,1-*b*]-1,3,4-selenadiazoles (**7**).



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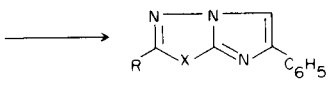

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a: R = H, X = Se d: R = CF_3, X = Se
b: R = CH_3, X = Se e: R = CF_3, X = S
c: R = C_2H_5, X = Se

The physical data of 2-substituted-6-phenylimidazo-[2,1-*b*]-1,3,4-selenadiazoles (**7**) are summerized in Table II.

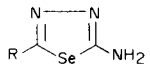
EXPERIMENTAL (9)

2-Amino-1,3,4-selenadiazole (**4a**).

Method A.

To a mixture of 2.76 g. (0.02 mole) of selenosemicarbazide (10), and 4.6 g. (0.1 mole) of 98% formic acid was added 7.65 g.

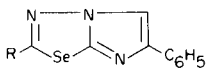
TABLE I



Compound	R	M.p. °C.	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found	λ max (a) (nm)	log ε
4a	H	177-178 (b)	65	$C_2H_3N_3Se$	16.21	16.17	2.02	2.10	28.37	28.41	261	2.59
4b	CH_3	228-230 (b)	75	$C_3H_5N_3Se$	22.22	22.29	3.08	3.00	25.92	25.88	260	2.67
4c	C_2H_5	202-203 (c)	78	$C_4H_7N_3Se$	27.27	27.30	3.97	3.89	23.86	23.72	261	2.70
4d	CF_3	235-236 (d)	70	$C_3H_2F_3N_3Se$	16.66	16.62	0.92	1.05	19.44	19.54	274	3.70
4e	C_6H_5	237-238 (e)	82	$C_8H_7N_3Se$	42.85	42.79	3.12	3.11	18.75	18.69	277	3.25

(a) In ethanol. (b) Crystallized from water. (c) Crystallized from ethanol-water. (d) Crystallized from acetic acid. (e) Crystallized from acetic acid-water.

TABLE II



Compound	R	M.p. (a) °C.	Yield %	Formula	C% Calcd.	C% Found	H% Calcd.	H% Found	N% Calcd.	N% Found	λ max (b) (nm)	log ε
7a	H	157-158	42	$C_{10}H_7N_3Se$	48.38	48.41	2.82	2.80	16.93	17.02	257	3.17
7b	CH_3	151-152	48	$C_{11}H_9N_3Se$	50.38	50.40	3.43	3.44	16.03	16.11	257	3.33
7c	C_2H_5	105-106	53	$C_{12}H_{11}N_3Se$	52.17	52.21	3.98	3.99	15.21	15.22	257	3.02
7d	CF_3	145-146	60	$C_{11}H_6F_3N_3Se$	41.77	41.72	1.89	1.83	13.29	13.30	257	3.19

(a) Crystallized from ethanol. (b) In ethanol.

(0.03 mole) of phosphorus oxychloride. The mixture, after standing at room temperature for one hour, was refluxed for ½ hour. The reaction mixture was then concentrated under reduced pressure, decomposed with 20 ml. of water and refluxed for one hour. The solution was neutralized with sodium hydroxide. The precipitate was filtered and crystallized from water to give 1.90 g. (65%) of **4a**; ν max cm^{-1}, 3130, 2950, 1600, 1490, 1430, 1325, 1000, 850, 775, 765, 690, nmr (dimethylsulfoxide), τ 0.77 (s, 1, CH) (this hydrogen which had two satellite was assigned to the ^{77}Se coupling (J = 55 Hz), 2.68 (br, 2, NH_2); m/e 148.

2-Amino-5-ethyl-1,3,4-selenadiazole (**4c**).

To a mixture of 2.76 g. (0.02 mole) of selenosemicarbazide and 2.96 g. (0.04 mole) of propionic acid was added 7.65 g. (0.03 mole) of phosphorus oxychloride. The mixture was refluxed for ½ hour, the excess phosphorus oxychloride was removed under reduced pressure, and the residue was decomposed by ice water. The precipitate was filtered and crystallized from acetic acid to give 2.8 g. (79%) of 2-propionamido-5-ethyl-1,3,4-selenadiazole (**3c**), m.p. 218-219°; ν max cm^{-1}, 1670 (C=O, amide); nmr (trifluoroacetic acid) τ 6.9 (q, 2, CH_2) 7.5 (q, 2, $COCH_2$), 8.75 (t, 3, CH_3), 8.97 (t, 3, CH_3); m/e 232.

Anal. Calcd. for $C_7H_{11}N_3OSe$: C, 36.20; H, 4.74; N, 18.10. Found: C, 36.20; H, 4.81; N, 18.15.

The amide was hydrolyzed by 2 hours refluxing with an excess of 15% hydrochloric acid and subsequent neutralization with sodium hydroxide. The precipitate was crystallized from aqueous ethanol to give 2.46 g. (75% overall yield) of **4c** (see Table I).

2-Amino-5-methyl-1,3,4-selenadiazole (**4b**).

Method B.

A mixture of 2.76 g. (0.02 mole) of selenosemicarbazide and 2 g. (0.02 mole) of acetic anhydride in 25 ml. of dry chloroform was refluxed for 4 hours. After cooling, the precipitate was filtered and crystallized from ethanol to give 3 g. (84%) of 1-acetylselenosemicarbazide (**8**), m.p. 183-184°.

Anal. Calcd. for $C_3H_7N_3OSe$: C, 20.00; H, 3.88; N, 23.33. Found: C, 20.06; H, 3.82; N, 23.45.

1-Acetylselenosemicarbazide was cyclized by one hour refluxing with an excess of acetyl chloride and subsequent hydrolysis of the amide as described for **4c**. The overall yield was 72% and the compound was found to be identical with a sample prepared by Method A.

2-Trifluoromethyl-6-phenylimidazo[2,1-*b*]-1,3,4-selendiazole (**7d**).

2-Amino-5-trifluoromethyl-1,3,4-selenadiazole 2.16 g. (0.01 mole) and 1.54 g. (0.01 mole) of 2-chloroacetophenone in 30 ml. of 95% alcohol was refluxed for 2 hours. After evaporation of the solvent, the residue was crystallized from ethanol to give 2.9 g. (80%) of **6d**, m.p. 202-203°.

Anal. Calcd. for $C_{11}H_9ClF_3N_3OSe$: C, 35.62; H, 2.42; N, 13.29. Found: C, 35.66; H, 2.39; N, 13.22.

Compound **6d** was refluxed with 70 ml. of water for 2 hours. After cooling, the precipitate was filtered and crystallized from ethanol to give 1.9 g. (60% overall yield) of **7d**, m.p. 145-146°; ν max cm^{-1}, 2590, 1510, 1460, 1430, 1400, 1280, 1200, 1080, 980, 795, 770, 725, 690; m/e 316.

The compounds **7a-c** were prepared similarly.

2-Trifluoromethyl-6-phenylimidazo[2,1-*b*]-1,3,4-thiadiazole (**7e**).

This compound was prepared similarly to **7d** from 2-amino-5-trifluoromethyl-1,3,4-thiadiazole (11), m.p. 166-167°; ν max cm^{-1}, 2950, 1495, 1455, 1430, 1410, 1310, 1200, 1185, 1135, 1100, 1050, 810, 770, 745, 720, 690; m/e 269.

Anal. Calcd. for $C_{11}H_6F_3N_3S$: C, 49.07; H, 2.23; N, 15.61. Found: C, 49.11; H, 2.27; N, 15.49.

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