STUDY OF ELECTROPHILIC SUBSTITUTION AND OXIDATION REACTIONS OF 4- AND 5-HYDROXYBENZO-2,1,3-SELENA-DIAZOLES

I. A. Belen'kaya, S. A. Sirik, Yu. E. Shapiro, and E. K. D'yachenko

The halogenation, nitrosation, and oxidation of 4- and 5-hydroxybenzo-2,1,3-selenadiazoles have been studied, as has the acetylation of these hydroxy compounds and their halogen and nitroso derivatives. The structure of the resulting compounds has been demonstrated, and it has been found that the nitroso-substituted derivatives exist primarily in the tautomeric oxime form.

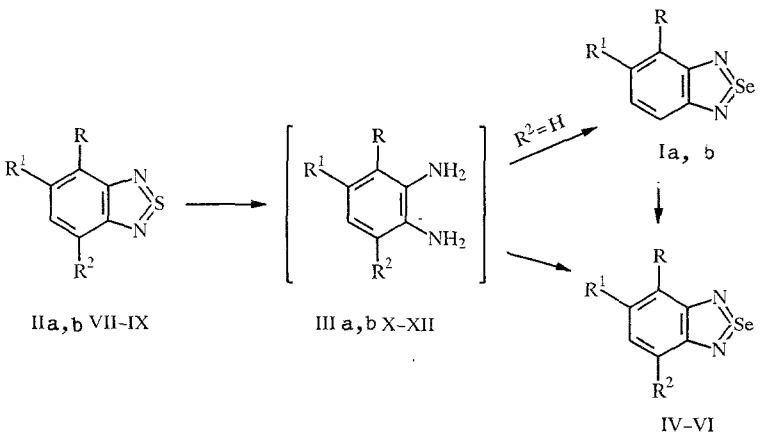
4- and 5-Hydroxybenzo-2,1,3-selenadiazoles (Ia, b) are difficult compounds to prepare and, therefore, their electrophilic substitution and oxidation reactions have hardly been studied. In the present study we have improved the method of preparing the hydroxy derivatives Ia, b as described in [1] by increasing their yield from 15-38% to 60-80% respectively, and we have studied certain electrophilic substitution and oxidation reactions of these compounds.

Reduction desulfurization of 4- and 5-hydroxybenzo-2,1,3-thiadiazoles (IIa, b) with iron in 10% hydrochloric acid gives, respectively, 2,3-diamino- and 3,4-diaminophenols (IIIa, b), which are condensed with selenious acid and converted to the hydroxy compounds Ia, b.

It should be noted that compound Ia could not be synthesized by a Bucherer reaction from 4-aminobenzo-2,1,3-selenadiazole in a manner like that of hydroxy derivative IIa by the method described in [2].

Chlorination of hydroxy derivatives Ia, b with sulfuryl chloride in acetic acid gives 4-hydroxy-5,7-dichloro- and 4-chloro-5-hydroxybenzo-2,1,3-selenadiazoles (IV and V) respectively. On bromination of compound Ib, 4-bromo-5-hydroxybenzo-2,1,3-selenadiazole (VI) is formed. We have established the structure of the halohydroxy derivatives IV-VI in the following manner. 4-Hydroxy-5,7-dichloro-, 4-chloro-5-hydroxy-, and 4-bromo-5-hydroxybenzo-2,1,3-thiadiazoles (VII-IX) of known structure, as reported in [4], were made to undergo reductive desulfurization in a similar manner to the thiadiazoles IIa, b. Condensation with selenious acid of the corresponding halogen-substituted aminophenols thus obtained gave compounds IV-VI.

On acetylation of hydroxy derivatives Ia, b and IV-VI with acetic anhydride in the presence of triethylamine, 4- and 5-acetoxy-, 5,7-dichloro-4-acetoxy, 4-chloro-5-acetoxy-, and 4-bromo-5-acetoxybenzo-2,1,3-selenadiazoles (XIIIa, b, XIV-XVI)



I—III a R=OH, $R^1=R^2=H$; b R=R^2=H, R^1=OH; IV, VII, X R=OH, $R^1=R^2$=Cl; V, VIII, XI R=Cl, R^1=OH, R^2=H; VI, IX, XII R=Br, R^1=OH, R^2=H

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TABLE 1. Properties of Benzo-2,1,3-selenadiazoles Ia, b, IV-VI, XIIIa, b, XIV-XVI, and XVIIa,b

Compound	Empirical formula	mp, °C*	R_f (system)[2*]	IR spectrum, ν, cm^{-1}	Yield, % (method)[2*]
Ia	$C_6H_4N_2OSe$	203...205[3*]	0,65 (A)	3517 (C—OH)	82 (1), 36 (2)
Ib	$C_6H_4N_2OSe$	206...208[3*]	0,58 (A)	3575 (C—OH)	62 (1)[4*], 45 (2)
IV	$C_6H_2Cl_2N_2OSe$	205...207	0,70 (B)	3511 (C—OH)	92 (1), 12 (2)
V	$C_6H_3ClN_2OSe$	254...256	0,61 (B)	3515 (C—OH)	79 (1), 45 (2)
VI	$C_6H_3BrN_2OSe$	213...215	0,61 (B)	3492 (C—OH)	74 (1), 25 (2)
XIIIa	$C_8H_6N_2O_2Se$	60...62[5*]	0,80 (A)	1750 (C=O)	83
XIIIb	$C_8H_6N_2O_2Se$	179...181	0,83 (A)	1750 (C=O)	81
XIV	$C_8H_4Cl_2N_2O_2Se$	148...152	0,65 (B)	1772 (C=O)	86
XV	$C_8H_5ClN_2O_2Se$	168...169	0,78 (C)	1767 (C=O)	90
XVI	$C_8H_5BrN_2O_2Se$	183...185	0,61 (B)	1756 (C=O)	89
XVIIa	$C_6H_3N_3O_2Se$	Decomp. without melting[6*]	0,48 (B)	1700 (C=O), 1640 (C=N—)	72
XVIIb	$C_6H_3N_3O_2Se$	The same	0,44 (B)	1700 (C=O), 1650 (C=N—)	100

*Compounds Ia, b and IV-VI were recrystallized from toluene, XIIIa, b and XIV were crystallized from a 1:2 ethanol—water mixture, XVI was crystallized from hexane, compound XV was purified by passing an acetone solution through a column filled with silica gel LSL254 5/40.

2*For composition of systems and different experimental methods, see Experimental.

3*According to the results of [1], compound Ia has mp 186-187°C and compound Ib has mp 202-205°C.

4*Yield can be increased by 15-20% through extraction of compound Ib from the filtrate with chloroform.

5*According to the results of [5], compound XIIIa has mp 60-66°C (decomp.).

6*Compounds XVIIa, b were not obtained in an analytically pure state.

TABLE 2. PMR Spectroscopic Data for Compounds XVIIIa, XIX-XXI

Compound	Chemical shifts, δ, ppm				$J_{H_AH_B}$, Hz
	H_A	H_B	COOH	CH_3	
XVIIIa	6,757	8,105	—	2,365	10,6
XIX	6,282	7,948	3,98	—	11,8
XX	6,584	7,238	3,58	—	11,8
XXI	6,413	7,337	3,82	—	12,0

are formed respectively, and their IR spectra are given in Table 1.

An attempt to carry out a Fries rearrangement with the acetoxy derivatives XIIIa, b was not successful. As a result of the reaction of these compounds with anhydrous aluminum chloride in nitrobenzene with subsequent removal of the latter from the reaction mixture by steam distillation, hydroxy compounds Ia, b were isolated from the reaction mixture rather than 4-hydroxy-7-acetyl- and 5-hydroxy-4-acetylbenzo-2,1,3-selenadiazoles, respectively.

Nitrosation of compounds Ia, b with sodium nitrite in acetic acid results in the formation of 4-hydroxy-5-nitroso- and 5-hydroxy-4-nitrosobenzo-2,1,3-selenadiazoles (XVIIa, b) respectively. It was not possible to carry out the nitrosation of hydroxy derivatives Ia, b under the conditions described in [6] for the nitrosation of IIa, b.

It should be noted that in the nitrosation of selenadiazole Ia, the nitroso group is only introduced into the 5-position, while in the nitrosation of thiadiazole IIa the nitroso group enters both the 5-position and the 7-position to form two products [7]. In the IR spectra of the nitroso compounds XVIIa, b there are bands at 1700 cm^{-1} which can be attributed to stretching vibrations of the C=O group and bands correspondingly at 1640 and 1650 cm^{-1} that are characteristic of vibrations of the C=N group in oximes. This suggests that the tautomeric keto form predominates in compounds XVIIa, b. The same pattern

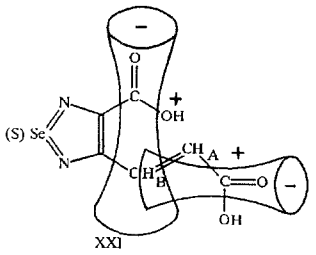


Fig. 1

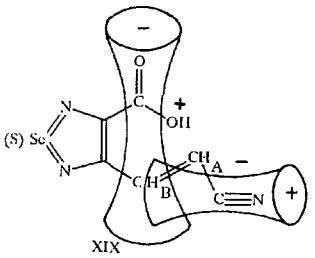


Fig. 2

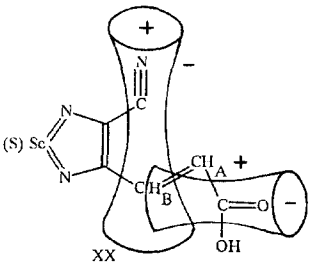
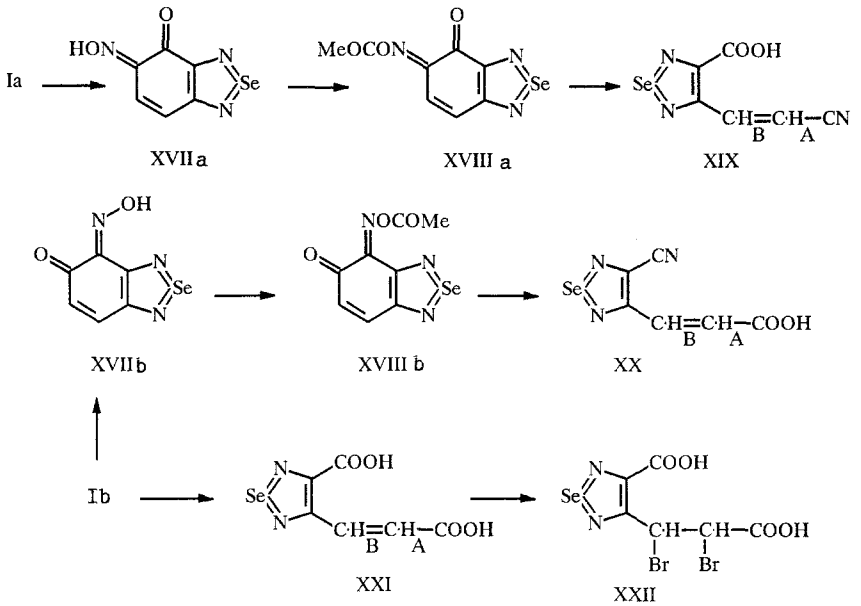


Fig. 3

occurs in the IR spectrum of 4-hydroxy-5-nitrosobenzo-2,1,3-thiadiazole as described in [8], but it is not a feature of the spectrum of 4-nitroso-5-hydroxybenzo-2,1,3-thiadiazole, which is reported in the same study.

Nitroso compounds XVIIa, b react with acetic anhydride to form the corresponding acetoximes XVIIIa, b, which on heating with a 1% solution of sodium hydroxide are converted to 3-(3-carboxy-1,2,5-selenadiazol-4-yl)acrylonitrile (XIX) and 3-(3-cyano-1,2,5-selenadiazol-4-yl)acrylic acid (XX) respectively.



It should be noted that nitriles XIX and XX are formed under more severe conditions than the corresponding thiadiazole nitriles [9], and even prolonged heating of the acetoxime XVIIIa in an alkaline medium (4 h instead of 3 min as indicated in [9]) does not lead to its complete conversion to nitrile XIX. According to the PMR data, XIX contains 9.8% of the initial acetoxime XVIIIa (Table 2).

On oxidation of hydroxy derivative Ia with a 30% solution of hydrogen peroxide in glacial acetic acid in the presence of sodium molybdate, 3-(3-carboxy-1,2,5-selenadiazol-4-yl)acrylic acid (XXI) is isolated, and when reacted with bromine the latter is converted to 2,3-dibromo-3-(3-carboxy-1,2,5-selenadiazol-4-yl)propionic acid (XXII).

The PMR spectroscopic parameters of compounds XIX-XXI that are given in Table 2 are virtually no different from the spectra of the analogous compounds containing a sulfur atom instead of a selenium atom that were reported in [9]. The good

agreement between the chemical shifts and vicinal spin—spin coupling constants of the olefinic protons (AB-type spin system) of the selenium- and sulfur-containing compounds of this series is an indication that these atoms have the same type of bonding molecular orbitals.

On replacing a carboxyl group in compound XXI with a nitrile and changing to compounds XIX and XX, the signals due to protons H_A and H_B are shifted to higher or lower field depending on the position of the nitrile group (see Table 2). This phenomenon was found previously in [9] for the sulfur-containing compounds but could not be explained. We attribute this effect to the difference in the magnetic anisotropy $\Delta\chi$ between the carbonyl and nitrile groups (Figs. 1-3), where a plus sign corresponds to a shielding effect of the protons situated within the corresponding zone. The difference between the chemical shifts of the protons H_A and H_B is governed by the different magnetic contribution $\Delta\sigma$ according to the McConnell equation [10].

It follows from the chemical shifts of the olefinic protons and their interpretation in terms of the magnetic anisotropy of the C=O and C≡N bonds that in compounds XIX-XXI the acrylic residue has an (S)-trans conformation (at room temperature), and all residues containing multiple bonds are conjugated with the selenadiazole ring, as is shown in Figs 1-3.

It has been demonstrated that the hydroxyhalo derivatives IV-VI and acids XX-XXII have selective fungicidal activity.* Compounds V and VI at a concentration of 0.1% cause 72% inhibition of the development of tomato phytophthora on green plants, while at a concentration of 0.003% they suppress the growth of the fungal mycelium of *Venturia inaegualis* and *Aspergillus niger* by 50%.

In a similar manner hydroxy compound IV inhibits the growth of the mycelium of *Fusarium monoliforme* by 60%. Acids XX-XXII at a concentration of 0.1% completely suppress the germination of spores of millet smut and also decrease tomato phytophthora and gray mold in beans by 55-85%

EXPERIMENTAL

IR spectra were recorded on a Specord IR-75 spectrometer in absolute chloroform or petrolatum oil. PMR spectra were obtained on a Bruker AM-250 spectrometer (250 MHz) for solutions in DMSO-d_6 at a concentration of 0.1 moles/liter. Chemical shifts are given relative to TMS.

The reaction was monitored and the purity of the compounds was assessed using TLC on Silufol UV-254 plates in the following systems: A) acetone—chloroform—hexane (2:1:2); B) benzene—acetic acid—acetone (100:1:50); C) acetone—toluene—petroleum ether (1:1:2); D) ethyl acetate—formic acid—hexane (45:6:15).

The properties of hydroxy compounds Ia, b and IV-VI, acetoxy derivatives XIIIa, b and XIV-XVI, and nitroso compounds XVIIa, b are shown in Table 1.

The PMR spectroscopic data for compounds XVIIIa and XIX-XXI are given in Table 2.

4-Nitrobenzo-2,1,3-selenadiazole was synthesized by the method of Éfros et al. [3]. 4-Aminobenzo-2,1,3-selenadiazole was obtained as described in [4] or by hydrolysis of 4-acetylaminobenzo-2,1,3-selenadiazole.

The C, H, and N elemental analysis data for the compounds listed in Table 1, and also for compounds XVIIIa, b and XIX-XXII matched the calculated values.

Hydroxybenzo-2,1,3-selenadiazoles Ia, b. Method 1. To 5 g (33 mmoles) of compound IIa or IIb in 100 ml of 10% hydrochloric acid was added 10 g (178.55 mmoles) of iron, avoiding vigorous foaming. The reaction mixture was then boiled for 20 min, filtered when hot, and the precipitate on the filtrate was washed with 500 ml of hot water (when there was a precipitate in the filtrate the latter was filtered repeatedly). The resulting filtrate was mixed with a solution of 7 g (54.5 mmoles) of selenious acid in 50 ml of water. The precipitate of selenadiazole Ia or Ib was filtered off, washed with water until neutral reaction, and dried. **Method 2.** To 1.24 g (6.39 mmoles) of compound XIIIa or XIIIb in 8.5 ml of nitrobenzene at 60°C was added 1.4 g (10.5 mmoles) of anhydrous aluminum chloride, and the resulting mixture was maintained at the same temperature for 6 h with stirring. The mixture was then cooled and 17 ml of alcohol and 50 ml of water were added, after which the nitrobenzene was removed by steam distillation. The distillation residue was filtered while hot and a precipitate of compound Ia or Ib was formed on cooling from the filtrate

4-Hydroxy-5,7-dichloro- and 4-Chloro-5-hydroxybenzo-2,1,3-selenadiazole (IV, V) Method 1. To a mixture of 1 g (5.03 mmoles) of compound Ia in 10 ml (174.8 mmoles) of acetic acid was added 1.2 ml (14.82 mmoles) of sulfuryl chloride.

*The experiments were carried out by Zh. S. Dyachina, to whom the authors with to express their gratitude.

The reaction mixture was kept for 20 min at 60-65°C, then cooled, and poured into water. The precipitate of IV was filtered off, washed with water, and dried at room temperature. Compound V was obtained in a similar manner using half the quantity of sulfuryl chloride. **Method 2.** To 1 g (4.52 mmoles) of compound VII or 1 g (5.36 mmoles) of compound VIII in 20 ml of 10% hydrochloric acid was added 2 g (35.71 mmoles) of iron, avoiding vigorous foaming. The reaction mixture was boiled for 20 min, then filtered while hot. The precipitate on the filter was washed with 100 ml of hot water. The combined filtrate was mixed with a solution of 1.4 g (10.9 mmoles) of selenious acid in 10 ml of water, and the resulting precipitate of selenadiazole IV or V was filtered off, washed with water, and dried.

4-Bromo-5-hydroxy-2,1,3-selenadiazole (VI). Method 1. Compound Ib (5 g, 22.15 mmoles) was mixed with 50 ml (874.15 mmoles) of acetic acid and 0.75 ml (29.1 mmoles) of bromine. The mixture was boiled for 20 min, then cooled to room temperature, and poured into 250 ml of water. The precipitate of selenadiazole VI was filtered off, washed with water, and dried. **Method 2.** Compound VI was obtained in a similar manner to compounds IV and V (method 2) from 1 g (4.33 mmoles) of thiadiazole IX.

Acetoxybenzo-2,1,3-selenadiazoles XIIIa, b and XIV-XVI. A mixture of 1 g of one of compounds Ia, b or IV-VI, 7 ml (74 mmoles) of acetic anhydride, and 0.1 ml (0.7 mmoles) of triethylamine was boiled for 20 min, then cooled, and poured into ice. The resulting precipitate of acetate was filtered off, washed with water, and dried. When the acetate separated as an oil, the reaction mixture was extracted twice with chloroform, and the combined extract was filtered and the solvent removed. The residue of acetate crystallized out on external cooling with ice.

4-Hydroxy-5-nitroso- and 5-Hydroxy-4-nitrosobenzo-2,1,3-selenadiazoles (XVIIa, b). To a suspension of 1 g of hydroxy derivative Ia (5.03 mmoles) in 20 ml of acetic acid at room temperature was added 0.85 g (11.97 mmoles) of sodium nitrite in 17 ml of water. The reaction mixture was stirred for a further hour and then diluted with 60-80 ml of water. The resulting precipitate of XVIIa was filtered off, washed with water, and dried. Compound XVIIb was obtained in a similar manner.

5-O-Acetyloxime of 4,5-Dioxo-4,5-dihydrobenzo-2,1,3-selenadiazole (XVIIIa, $C_8H_5N_3O_3Se$). A mixture of 1.14 g (5 mmoles) of compound XVIIa and 16 ml of acetic anhydride was kept for 4 days at room temperature. Then the precipitate which had formed was filtered off, washed with 5-10 ml of ether, and dried. The yield was 1.15 g (85%) of compound XVIIIa, which on heating swelled up and burst into flames without melting; R_f 0.59 (B).

4-O-Acetyloxime of 4,5-Dioxo-4,5-dihydrobenzo-2,1,3-selenadiazole (XVIIIb, $C_8H_5N_3O_3Se$). A mixture of 1.14 g (5 mmoles) of compound XVIIb and 8 ml of acetic anhydride was kept for 2 days at room temperature. The precipitated product was filtered off, washed with 5-10 ml of ether, and dried. The yield was 1.2 g (89%) of compound XVIIIb, which on heating swelled up and burst into flames without melting; R_f 0.6 (B).

3-(3-Carboxy-1,2,5-selenadiazol-4-yl)acrylonitrile (XIX, $C_6H_3N_3O_2Se$) and 3-(3-Cyano-1,2,5-selenadiazol-4-yl)acrylic Acid (XX, $C_6H_3N_3O_2Se$). A mixture of 1.1 g (4.1 mmoles) of acetoxime XVIIIa or XVIIIb and 25 ml of a 1% solution of sodium hydroxide was heated on a boiling water bath for 4 h. The reaction mixture cooled to room temperature was supplemented with 18% hydrochloric acid until pH 3-4 was reached and extracted with chloroform (6 × 10 ml). The aqueous layer was acidified to pH 1 and repeatedly extracted with ether. The combined ether extract was filtered, and after removal of ether yielded 0.25-0.4 g (27-43%) of product XIX or XX. Nitrile XIX: mp 187-189°C (acetone—toluene, 1:4); R_f 0.80 (D). Acid XX: mp 119-121°C (benzene—petroleum ether, 1:1); R_f 0.87 (D).

3-(3-Carboxy-1,2,5-selenadiazol-4-yl)acrylic Acid (XXI, $C_6H_4N_2O_4Se$). A mixture of 1.3 g (6.53 mmoles) of selenadiazole Ib, 0.01 g (0.04 mmole) of sodium molybdate, and 15 ml of glacial acetic acid was heated to 45°C, then 10 ml of 30% hydrogen peroxide was added to it with stirring, and the mixture was left at room temperature for 4.5 days. Then 33 ml of distilled water was added to the reaction mixture, unreacted Ib and by-products were filtered off after 2.5 h, and the filtrate was repeatedly extracted with ether. The ether extract was filtered and the ether removed. The yield was 0.56 g (35%) of acid XXI, mp 183-184°C (acetone—toluene, 1:4); R_f 0.81 (D).

2,3-Dibromo-3-(3-carboxyl-1,2,5-selenadiazol-4-yl)propionic Acid (XXII, $C_6H_2Br_2N_2O_4Se$). Acid XXI (0.123 g, 0.5 mmole) was placed in a weighing bottle on a watch glass, 0.25 ml (4.85 mmoles) of bromine was added to it, and the mixture was left in the closed bottle at room temperature for 2 days. The bottle was then opened, the excess bromine evaporated off, and on the glass remained 0.203 g (100%) of compound XXII, which was purified in the following manner. It was heated to boiling in toluene, the hot solution was filtered, ethanol was added to the filtrate until it became slightly turbid, and it was left for several days until a precipitate had formed. The precipitate was filtered off and dried, yielding acid XXII, mp 177-179°C.

4-Acetylaminobenzo-2,1,3-selenadiazole (XXIII). A mixture of 9.36 g (41.05 mmoles) of 4-nitrobenzo-2,1,3-selenadiazole, 12 g of reduced iron, 30 ml of acetic anhydride, and 10 ml of ethanol was boiled for 30 min. Then 200 ml of ethanol was added to the hot reaction mixture, the mixture was brought to the boil and filtered. The hot precipitate on the filter was washed with

100 ml of hot ethanol. The filtrate was concentrated to 50 ml and 500 ml of water was added to the residue. The acetylamine which separated out was filtered off, dissolved in chloroform, and filtered. After removal of the chloroform, 5.85 g (59.4%) of selenadiazole XXIII was obtained, mp 177-179°C (from ethanol); IR spectrum (KBr pellet): 1665 cm^{-1}; R_f 0.67 (B).

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