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Facile Synthesis of 2,2'-Dichalcogenobis (N-Alkyl/Aryl Benzenesulfonamides) from N-Substituted benzenesulfonamides and the Emergence of 2-Alkyl 1, 3, 2-Benzothiaselenazole 1,1 dioxides. Ebselen Analogues.

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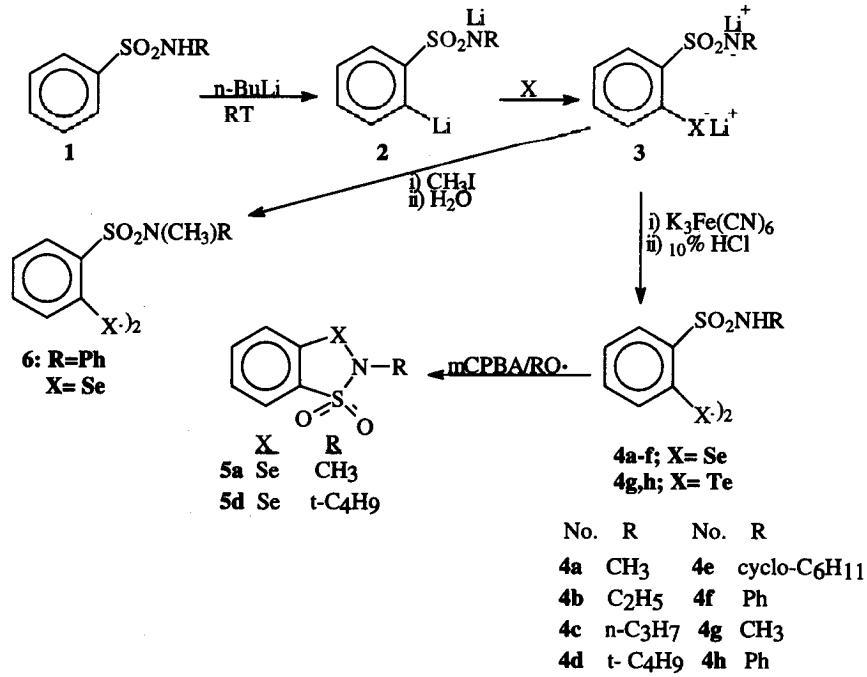
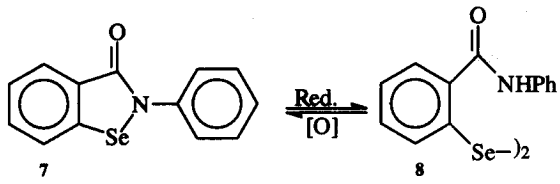
Abstract: A one pot synthesis of 2-2'-diselenobis/ditellurobis(N-alkyl/aryl benzenesulfonamides) 4a-h from N-alkyl/aryl benzenesulfonamides is elaborated. The first cyclization of 2-2' -diselenobis (N-methyl benzenesulfonamide) 4a into 2- methyl-1,3,2-benzothiaselenazole 1,1 dioxide (5a)[1a] using 3-chloroperoxybenzoic acid is described. Compounds 4a-h and 5a and d act as a new class of biologically active[1b] compounds. © 1997 Elsevier Science Ltd.

Many clinical pathological conditions are accompanied or even caused by oxidative stress which is characterised by a situation that more reactive oxygen species are formed than can be counteracted by the antioxidant defense system of the organism.[2] Inflammatory conditions linked to lipid peroxidation and its products, formed either enzymatically or by auto-oxidation include certain carcinomas, rheumatoid arthritis, burns, shock, post ischaemic necrosis, psoriasis and asthma, Parkinson's disease, epilepsy and neuronal ceroid lipofuscinosis, liver cirrhosis and radiation damage.[3] In these conditions and other diseases such as myocardial infarction and atherosclerosis, chronic renal failure, phenyl ketonurea, muscular dystrophy, sudden child death, cystic fibrosis, cataracts, diabetes, Down's syndrome, Keshan's disease, Kwashiorkor, congestive heart failure in children and young women, growth and mental retardation, depleted selenium levels and/or low glutathione peroxidase activities in humans have been observed.[4] In a number of the above cases selenium supplementation was claimed to improve the condition.[3,4] Some seleno-organic compounds have also been found to be antiviral,[5] antimalarial[6] and cytokine inducers where the reference compound has been preferentially ebselen.[5,7,8,9] Interferons (α, β and γ) are known to inhibit many different RNA and DNA viruses while tumor necrosis factors are known to be potent especially during tumor growth, bacterial and parasitic infections. Earlier findings confirmed that the elements oxygen, sulfur, selenium and probably tellurium have immunomodulatory activities.[10] It would therefore be rational to look for these element combinations to redress the above mentioned epidemics and such projections are at the heart of this synthetic work.

The search by scientists to find seleno-organic compounds such as ebselen and some of its analogs[8-14] which utilize the particular redox properties of selenium as a novel approach to curing the above epidemics looks promising. Selenium occupies a special position between metals and non-metals and shows a strong tendency to undergo redox reactions in reducing and oxidizing media. It has been precisely ascertained that it is this particular property of selenium in the form of selenocysteine which is found in selenium-containing enzymes of biological importance such as glutathione peroxidase and glycine reductase.[15a,b] Small synthetic molecules having selenium capable of showing such redox properties could act as glutathione peroxidase mimics.[7,16,17] A lot of organo-selenium compounds have been synthesized which exhibit some striking biological activities but cannot be developed into useful pharmaceuticals because of their high toxicity.[3] Ebselen is the only seleno-organic compound whose vast range of biological actions are quite well known which are characterised by efficacy, low toxicity and lack of undesired side effects. Models set by this molecule, ebselen, whose biological actions have been unraveled and summarized[16,17] could be considered routine for new compounds **4** and **5.**



Scheme 1



7 8

Scheme 2

In this work, synthesis of a new heterocyclic system **5a** and **d** and related metabolites **4a-h** (scheme 1) especially those resembling ebselen(**7**) and its derivative, 2,2'-diselenobis(N-phenylbenzamide)(**8**) (scheme 2) is reported. This has opened up a new synthetic era of bio-active compounds[1b] in the search for improved tolerance and less toxic molecules to humans through synergism by incorporation of elements of the same group i.e. oxygen, selenium and sulfur and oxygen, tellurium and sulfur. The ability of telluro-organic compounds to behave in the same manner as seleno-organic compounds with respect to biological activities looks promising in this class of compounds.[1b]

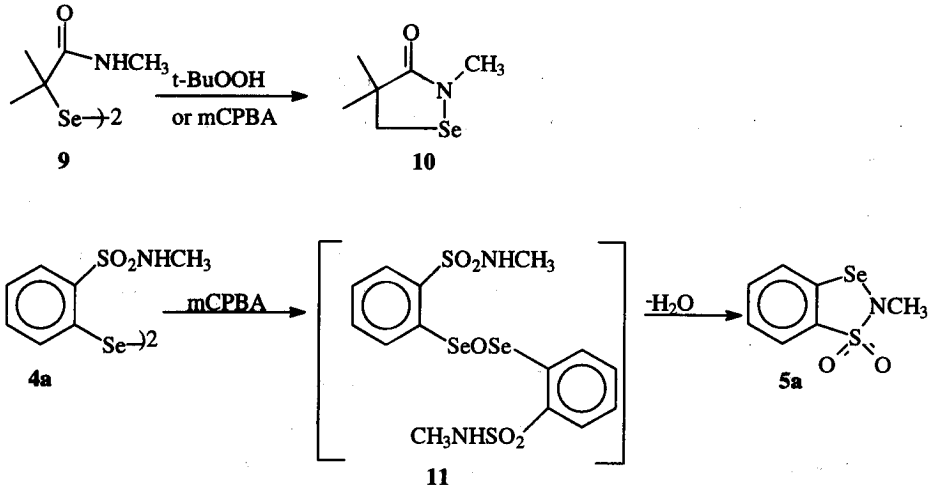
N-substituted alkyl and aryl benzenesulfonamides have been known to undergo ortholithiation reactions[19-21] and the chalcogens sulfur, selenium and tellurium are known to readily insert into the carbon-lithium bond[13, 14, 18]. This synthetic utility has been used in my synthetic work to insert selenium and tellurium into the carbon-lithium bond of the dianion intermediate **3**.

RESULTS AND DISCUSSION

The N-substituted benzenesulfonamides (**1**) were conveniently ortholithiated with excess n-butyllithium at room temperature in tetrahydrofuran under a slow stream of nitrogen giving the dilithiosulfonamides **2**. Addition of selenium or tellurium to this intermediate resulted in the expected insertion of the chalcogen into the carbon lithium bond giving dianion intermediates **3**. Treatment of **3f** with methyl iodide preferentially led to N-methylation yielding compound **6**. No methylation was observed at the selenium atom. Good yields of compounds **4a-f** (80-91%) were obtained by treatment of intermediate species **3a-f** with iron(III) which easily oxidized the selenolate(Se^{-1}) and the tellurolate(Te^{-1}) anionic species into the diselenide(Se^{0}) and ditelluride(Te^{0}) respectively as was previously observed.[13]

Compounds **4a, 4b** and **4g** showed more than one peak for the secondary sulfonamide functional group(NH) above 3265 cm^{-1}(IR/KBr). This phenomenon was unique for small aliphatic groups attached to the nitrogen atom of system **4** leading to more than one possible conformation about the C-Se-Se-C and C-Te-Te-C linkages. Only one conformation was detectable for the same compounds in solution by ^{1}HNMR probably

signaling the existence of one stable conformation. Elementary analysis showed high purity of the compounds while infrared spectra of the N-substituted benzenesulfonamides(substrates) showed a single peak for -NH- group of the secondary sulfonamide focusing the origin of the structural conformations on diselenide and ditelluride linkages given above.

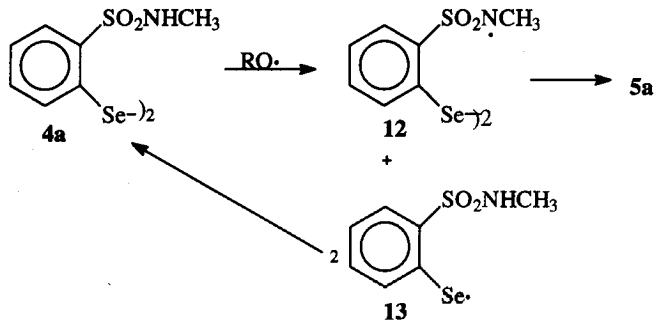


Scheme 3

Diselenides are known to be oxidized by ozone or t-butyl hydroperoxide into selenenic anhydrides, seleninic-selenenic anhydrides and seleninic anhydrides under anhydrous conditions.[22a,b] It would therefore follow that this typical oxidation would occur whenever the diselenide linkage is the only functionality to be oxidized. This known practical procedure was employed to cyclize amide **9** into the isoselenazolidine-3-one **10** (scheme 3) using t-butyl hydroperoxide or 3-chloroperoxybenzoic acid under anhydrous conditions.[15b] Similarly, I used 3-chloroperoxybenzoic acid to induce cyclization of **4a** into **5a.** The rate determining step is likely to be the formation of the intermediate selenenic anhydride **11.** ^{1}HNMR showed the methyl group of **5a** as a singlet while that of **4a** was shown as a doublet and the nitrogen proton as a quartet. Monitoring of the progress of reaction by TLC during oxidation of **4b-f** into **5b-f** with 3-chloroperoxybenzoic acid indicated product formation but after column chromatography using CH_2Cl_2 as eluent the substrates were recovered.

Later, another route was established[23] and opened up several ways for the cyclization of compounds **4a** using known methods for amidyl radical generation[24](scheme 4). Formation of the amidyl radical **12** in the later case was confirmed by isolation of benzoic acid, **5a** and substrate(**4a**) signaling proton abstraction attached to nitrogen as the decisive step in the formation of **5a.** The substrate was always recovered in the latter case

probably due to reconstitution of the intermediate species **13** into **4a** as was indicated earlier by Fong and Schiesser (1995).



Scheme 4

tert-Butyl hypochlorite(N-chlorinating and radical generating reagent) was used to convert 2-2'-diselenobis(N-tert-butyl benzenesulfonamide) (**4d**) into 2-tert-butyl-1, 3, 2-benzothiaselenazole 1-1 dioxide(**5d**).

Experimental

General:

Reaction progress was monitored by analytical TLC on 0.2mm silica gel pre-coated glass plates without fluorescent indicator. Flash chromatography was conducted with Merck Silica gel 60, particle size 0.063-0.2mm. Melting points were determined in open tubes using digital melting point apparatus: Electrothermal IA9100 and are uncorrected. IR spectra were recorded on a Perkin-Elmer FT spectrometer. ^{1}HNMR spectra were recorded on Bruker 300MHz spectrometer.

All starting materials were purchased from Aldrich Chem. Co. and Fluka. N-alkyl/aryl benzenesulfonamides(**1**) were synthesized from benzenesulfonyl chloride and the corresponding amines according to standard procedures.[25] Tetrahydrofuran was freshly distilled from LiAl H_4.

2,2'-Diselenobis/ditellurobis (N-alkyl/aryl benzenesulfonamides)[26] (4a-h): General Procedure.

To a well stirred solution of sulfonamide (**1**) (22.6 mmol) in 150ml tetrahydrofuran in a dry flask under nitrogen was added a solution of 1.6M n-butyllithium(31 ml; 50 mmol) in hexane during 10 minutes and stirred for a further 30 minutes at room temperature. Selenium/tellurium (23 mmol, 1.82/2.93g) was then added in one portion and the mixture was stirred for 4 hours. Potassium ferricyanide solution (22.6 mmol, 7.4 g in100ml water) was added to the deep brown solution and stirred overnight, acidified with 100ml of 2M HCl, stirred for

a further 40 minutes and the organic layer was extracted using methylene chloride(3 x 50 ml). The solvent mixture was evaporated under reduced pressure and the products **4a-h** were isolated by column chromatography eluting first using methylene chloride as eluent. The compounds were recrystallized from methylene chloride-hexane.

2-2'-Diselenobis(N-methyl benzenesulfonamide) 4a. Yellow-orange crystals, mp. 184-186 °C. Yield: 4.5g(80%). IR/KBR $\nu_{max.}$ cm^{-1} 3348.78, 3279.69 (NH); 1320.67, 1158.44 (SO_2); ^{1}HNMR ($CDCl_3$ +DMSO): δ 2.636 (d, 3H, J=6.2Hz, CH_3); 6.236(q, 1H, J=4.8 and 5.1Hz, NH); 7.348-7.434(m, 2H, ArH); 7.858-7.930(m, 2H, ArH). Anal. Cald. for $C_{14}H_{16}N_2O_4S_2Se_2$(498.33): C, 33.74; H, 3.24; N, 5.62; S, 12.87. Found: C, 33.68; H, 3.18; N, 5.64; S, 13.10.

2-2'-Diselenobis(N-ethyl benzenesulfonamide) 4b. Yellow crystals, mp. 171-172 °C. Yield: 4.94g(83%). IR/KBr $\nu_{max.}$ cm^{-1}: 3314.94, 3268.28, (NH) ; 1318.84, 1158.52 (SO_2); ^{1}HNMR ($CDCl_3$ +DMSO): δ 1.001 (t, 3H, J=7.2Hz, CH_3) ; 2.916 (q, 2H, J=6 and 7.2Hz, CH_2) ; 6.217 (t, 1H, J=5.8 Hz, NH); 7.249-7.294 (m, 2H, ArH); 7.748-7.772 (m, 1H, ArH); 7.806-7.836 (m, 1H, ArH). Anal. Cald. for $C_{16}H_{20}N_2O_4S_2Se_2$(526.39): C, 36.51; H, 3.83; N, 5.32; S, 12.18. Found: C, 36.45; H, 3.80; N, 5.39; S, 12.11

2-2'-Diselenobis(N-propyl benzenesulfonamide) 4c. Yellow crystals, mp. 125-128 °C. Yield: 5.26g(84%). IR/KBR $\nu_{max.}$ cm^{-1} 3312.78 (NH); 1317.58, 1156 (SO_2); ^{1}HNMR (DMSO): δ 0.781(t, 3H, J=7.4 Hz, CH_3); 1.404(sext., 2H, CH_2) ; 2.850(q, 2H, J=6.7Hz, N-CH_2); 7.433-7.521(m, 2H, ArH); 7.788-7.865(m, 2H, ArH); 8.057(t, 1H, J=5.8Hz, NH). Anal. Cald. for $C_{18}H_{24}N_2O_4S_2Se_2$(554.44): C, 38.99; H, 4.36; N, 5.05; S, 11.56. Found: C, 38.76; H, 4.34; N, 5.18; S, 11.60.

2-2'-Diselenobis(N-tertbutyl benzenesulfonamide) 4d. Yellow crystals, mp. 207-209 °C. Yield: 5.79g(88%). IR/KBR $\nu_{max.}$ cm^{-1} 3303.94 (NH); 1312.71, 1146.48 (SO_2); ^{1}HNMR ($CDCl_3$): δ 1.249(s, 9H, CH_3); 5.168(s, 1H, NH); 7.339-7.413(m, 2H, ArH); 7.864-7.893 (m, 1H, ArH); 8.001-8.032(m, 1H, ArH).

Anal. Cald. for $C_{20}H_{28}N_2O_4S_2Se_2$(582.49): C, 41.24; H, 4.85; N, 4.81; S, 11.01. Found: C, 41.11; H, 4.95; N, 5.00; S, 11.08.

2-2'-Diselenobis(N-cyclohexyl benzenesulfonamide) 4e. Yellow crystals, mp. 210-212 °C. Yield: 6.53g(91%). IR/KBR $\nu_{max.}$ cm^{-1} 3304.66 NH ; 1318.83, 1158.13 (SO_2); ^{1}HNMR ($CDCl_3$): δ 1.187-1.233 (m, 5H, CH_2); 1.521-1.528 (m, 1H, CH_2); 1.626-1.747(m, 4H, CH_2); 3.151-3.254(m, 1H, N-CH-); 5.022(d, 1H, J=7.8Hz, NH); 7.384-7.426(m, 2H, ArH); 7.865-7.895(m, 1H, ArH); 7.982-78.012(m, 1H, ArH). Anal. Cald. for $C_{24}H_{32}N_2O_4S_2Se_2$(634.57): C, 45.43; H, 5.08; N, 4.41; S, 10.10. Found: C, 45.40; H, 5.10; N, 4.52; S, 9.90.

2-2'-Diselenobis(N-phenyl benzenesulfonamide) 4f. Orange crystals, mp. 154-155 °C. Yield: 5.70g(81%). IR/KBR $\nu_{max.}$ cm^{-1}: 3288.07 (NH); 1341.81, 1153.03 (SO_2); ^{1}HNMR (DMSO): δ 7.042-7.136(m, 3H, ArH); 7.246-7.325(m, 3H, ArH); 7.403 (dd, 1H, J=7.7 & 7.3Hz, ArH); 7.585 (d, 1H, J=7.8, ArH); 7.889(dd,

1H, J=1H, ArH); 10.770 (s, 1H, NH). Anal. Cald. for $C_{24}H_{20}N_2O_4S_2Se_2$(622.47): C, 46.31; H, 3.24; N, 4.5; S, 10.30. Found: C,46.11; H, 3.38; N, 4.47; S, 10.21.

2-2'-Ditellurobis(N-methyl benzenesulfonamide) 4g. Orange crystals, mp. 169-172 °C. Yield: 5.65g(82%). IR/KBR $\nu_{max.}$ cm^{-1}: 3348.90, 3279.63 (NH) 1317.15, 1154.64 (SO_2); ^{1}HNMR ($CDCl_3$): δ 2.662(d, 3H, J=5.5 Hz, CH_3); 5.135(q, 1H, J=5.2Hz, NH); 7.277-7.328 (m, 1H, ArH); 7.408-7.7.412 (m, 1H, ArH); 7.911 (dd, 1H, J=1.4 &1.5Hz, ArH); 8.091(dd, 1H, J=1.1 Hz, ArH).

Anal. Cald. for $C_{14}H_{16}N_2O_4S_2Te_2$(595.61): C, 28.23; H, 2.71; N, 4.70; S, 10.77. Found: C28.22; H, 2.70; N, 4.62; S, 10.70.

2-2'-Ditelellurobis(N-phenyl benzenesulfonamide) 4h. Orange crystals, mp. 152-154 °C. Yield: 6.83g(84%). IR/KBR $\nu_{max.}$ cm^{-1}: 3299.46 (NH); 1341.20m, 1330.19, 1152.44 (SO_2); ^{1}HNMR (DMSO): δ7.053-7.113(m, 3H, ArH); 7.233-7.292(m, 3H, ArH); 7.403-7.457 (m, 1H, ArH); 7.809-7.847 (m, 2H, ArH); 10.660 (s, 1H, NH). Anal. Cald. for $C_{24}H_{20}N_2O_4S_2Te_2$(719.76): C, 40.05; H, 2.81; N, 3.89; S, 8.91. Found: C,40.11; H, 3.00; N, 3.83; S, 8.84.

2-2'-Diselenobis(N-methyl-N- phenyl benzenesulfonamide) 6. After the formation of the dianion intermediate **3**(R=Ph) methyl iodide(5 ml) was added and the mixture stirred overnight. The mixture was mixed with water(100ml) and stirred a for further 2 hours. The solvent mixture was evaporated to dryness under reduced pressure, the product isolated by column chromatography eluting first using methylene chloride as eluent and recrystallised from methylene chloride-hexane as long white needles. Yield; 4.5g(61%). mp. 160-163 °C. IR/KBR $\nu_{max.}$ cm^{-1} : 1339.76, 1173.12 (SO_2); ^{1}HNMR ($CDCl_3$): δ3.357 (s, 3H, NCH_3); 7.183-7.216 (m, 2H, ArH); 7.273-7.388 (m, 5H, ArH); 7.613-7.683(m, 2H, ArH).

Anal. Cald. For $C_{26}H_{24}N_2O_4S_2Se_2$(650.54): C, 48.00; H, 3.72; N, 4.31; S, 9.86: Found; C,47.78; H, 3.86; N, 4.12; S, 9.76.

2-Methyl-1, 3, 2-benzothiaselenazole 1,1 dioxide[26](5a). To a well stirred solution of 2-2'-Diselenobis(N-methyl benzenesulfonamide) (0.85g; 1.7mmol.) in methylene chloride(30ml) cooled to -10 °C was added 3-chloroperoxybenzoic acid(1.2g; 86%; 6mmol.) in methylene chloride(50 ml) over a 45 minute period. The reaction was left to proceed for 24 hours while the temperature was allowed to rise to room temperature. Sodium carbonate(0.6g; 6mmol.) was added to the resulting mixture and stirred for further 24 hours. The solid was filtered off and washed using methylene chloride (3x50ml). The solvent was evaporated under reduced pressure and the product was isolated by column chromatography eluting first using methylene chloride as eluent. Product was recrystallised from hexane as white needles. Yield: 0.27g (32%). mp. 97-98 °C. IR/KBR $\nu_{max.}$ cm^{-1} : 1320.75, 1164.74 (SO_2); ^{1}HNMR ($CDCl_3$): δ3.505 (s, 3H, CH_3); 7.710-7.793(m, 2H, ArH); 7.855-7.909(m, 1H, ArH); 8.020-8.060 (m, 1H, ArH). ^{13}CNMR($CDCl_3$): δ 46.84 (CH_3); 126.04 (-CH-); 127.21 (-CH-

); 128.35 (CH-); 133.90 (-CH-); 131.94 (-C-);132.58 (-C-). Anal. Cald. For $C_7H_7NO_2SSe$(248.16): C, 33.88; H, 2.84; N, 5.64; S, 12.92: Found; C,33.74; H, 2.84; N, 5.70; S, 12.88

2-tert-Butyl-1, 3, 2-benzothiaselenazole 1,1-dioxide(5d). To a well stirred solution of 2-2'-diselenobis(N-tert-butyl benzenesulfonamide) (0.5g; 0.86mmol.) in methylene chloride(30 ml) was added tert-butyl hypochlorite(2 ml in 25 ml CH_2Cl_2) over 30 minutes. The stirring was continued for a further 3 hours. The solvent was evaporated under reduced pressure and **5d** was isolated by column chromatography eluting first using methylene chloride as eluent. Yield: 0.12g (24%). mp. 113-115 °C. IR/KBR $\nu_{max.}$ cm^{-1}: 1324.06, 1161.30 (SO_2); ^{1}HNMR ($CDCl_3$): δ 1.424 (s, 9H, CH_3); 7.409 (dd, 1H, J=7.5 and 7.6 Hz, ArH); 7.485-7.574 (m, 2H, ArH); 7.705(d, 1H, J=7.7 Hz, ArH). Anal. Cald. For $C_{10}H_{13}NO_2SSe$(290.24): C, 41.38; H, 4.51; N, 4.83; S, 11.02: Found; C,41.31; H, 4.60; N, 4.72; S, 10.88.[1]

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26. The nomenclature of compounds **4a-h** was according to ref. 24. The nomenclature of **5a, d** was accordingly deduced from the closely related systems: 1, 3, 2-oxathiazole and 3H-1, 2, 3-benzothiaselenazole(Katritzky, A. R. *Comprehensive Heterocyclic Chemistry*; Pergamon Press: Oxford, **1984,** (8) 932, 966.) and from the knowledge that the elements of group six are given order of preference from oxygen through tellurium and nitrogen comes last(Katritzky, A. R. *Handbook of Heterocyclic Chemistry*; Pergamon Press: Oxford, **1985,** 22).

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