Unusual Formation of 2-Aryl-7,7-dimethyl-6,8-epidiseleno-5,6,7,8-tetrahydro-5-quinazolones

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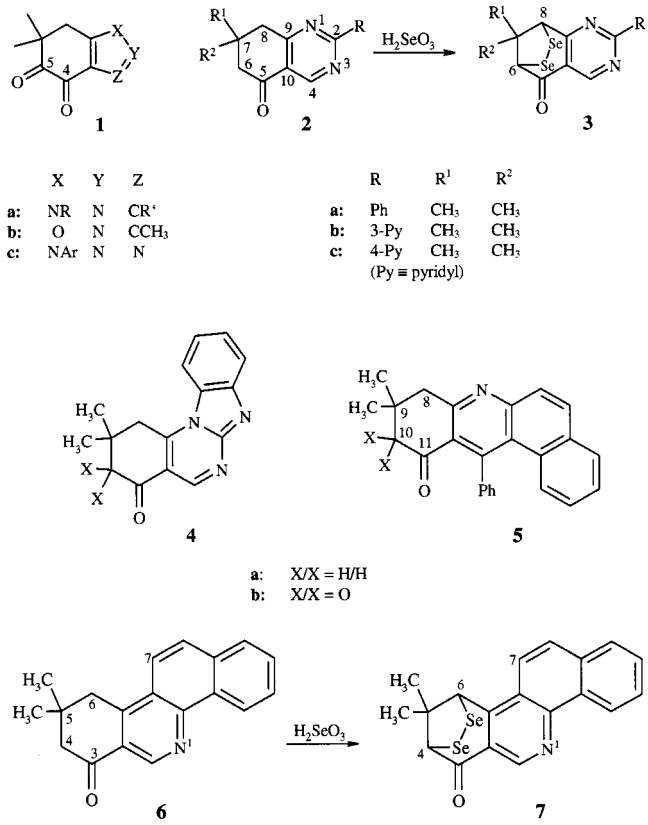
The selenious acid oxidation of 2-aryl-7,7-dimethyl-5,6,7,8-tetrahydro-5-quinazolones **2a–c** leads to the corresponding 2-aryl-7,7-dimethyl-6,8-epidiseleno-5,6,7,8-tetrahydro-5-quinazolones **3a–c**. This is the first observation of the formation of an intramolecular unsymmetrical diselenide by selenious acid oxidation and reports the first derivatives of the new ring system 2,3-diselenabicyclo[3.2.1]octane.

It has been shown earlier that selenious acid oxidation of various 6,6-dimethyl-4,5,6,7-tetrahydro-4-benzazolones, -indazolones, -indoxazenones, and -benztriazolones leads to the corresponding 4,5-dioxo derivatives **1a−b** exclusively[1−7] (Scheme 1).



Scheme 1. Structures **1−7**

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In contrast, however, selenious acid oxidation of the 2-aryl-7,7-dimethyl-5,6,7,8-tetrahydro-5-quinazolones **2a**,[8] **2b**, and **2c**[9] resulted in the formation of the corresponding 2-aryl-7,7-dimethyl-6,8-epidiseleno-5,6,7,8-tetrahydro-5-quinazolones **3a−3c**, although − exactly as in the case of the oxidation of 4,5,6,7-tetrahydro-4-indazolones − the oxidation of **2a−c** has been carried out in acetic acid with or without catalytic amounts of sulfuric acid.[3−5] The diselenides **3a** and **3c** were the only reaction products which could be separated by column chromatography or by recrystallization from acetic acid with yields of 36% and 37%, respectively. Our attempts to isolate and determine the structure of the other reaction products were not successful. The diselenide **3b** could not be obtained in pure form; very similar R_f values of the diselenide and its reaction admixtures were the reason. The percentage of the diselenide **3b** in its reaction mixtures was 60−70% as estimated by ^{1}H-NMR spectroscopy.

The electron-impact mass spectrum of compound **3c** is characterized by a relatively intensive molecular peak (20%) at m/z = 411 (^{80}Se). At the same time, the M^+ and Se_2^+ ions are the only selenium-containing ions appearing after the decomposition of **3c**. The fragmentation mainly occurs under decomposition of the most intense ion (base peak) formed by elimination of Se_2^+ from the molecular ion.

Table 1. ^{1}H-, ^{13}C, and ^{77}Se-NMR data of the diselenides **3** and **7**; δ in ppm, J in Hz; for each compound the upper now belongs to the −C^{8}HSe− and the lower to the −C^{6}HSe− fragment in the compounds **3** and −C^{6}HSe−/−C^{4}HSe− in compound **7**, respectively

		δ(^{77}Se)	δ(^{13}C)	δ(^{1}H)	$^2J_{Se,H}$	$^5J_{H,H}$	$^1J_{Se,C}$	$^1J_{Se,Se}$
3a	(8)	545	60.4	4.68	31.5	0.9	66.6	361.2
	(6)	368	62.9	4.18	28.8		67.5	
3b	(8)	547	60.2	4.67	31.9	1.0		
	(6)	367	62.8	4.18	28.5			
3c	(8)	549	60.2	4.69	33.6	1.0	65.9	360.5
	(6)	365	62.8	4.20	30.5		67.9	
7	(6)	564	53.6	5.30	31.9	0.7		
	(4)	415	62.8	4.27	29.1			

The structures of the diselenides **3a−c** were further confirmed by NMR-spectral data (^{1}H, ^{13}C, ^{77}Se). The ^{1}H and

  1434−193X/99/0707−1585 $ 17.50+.50/0

^{13}C resonances of the fragment $-C^6H-Se-Se-C^8H-$ are observed in the characteristic regions of $\delta = 4.1-4.7$ in the ^1H-NMR and $\delta = 60-63$ in the ^{13}C-NMR spectra accompanied by satellite signals due to ^{77}Se-^1H and ^{77}Se-^{13}C couplings, respectively (Table 1). The assignment of ^1H, ^{13}C, and ^{77}Se resonances is based on the mentioned couplings and was confirmed by HETCOR spectra of compounds **3a** and **3c** which revealed correlations between the carbonyl carbon atom (C-5, $\delta = 188.7$ and 187.4, respectively) and 6-H ($\delta = 4.18$ and 4.20, respectively). A stereochemical assignment of the two diastereotopic methyl groups in **3a−c** was not possible; the HETCOR spectrum, however, proves that the smaller ^1H- and ^{13}C-chemical shifts belong to one and the larger ones to the other methyl group.

The ^{77}Se-NMR spectra of **3** (and **7**; see below) showed two doublets of equal intensity due to the geminal coupling between the ^{77}Se nuclei and the methine protons 6-H and 8-H, respectively. The same coupling constant values were obtained from the ^{77}Se satellites in the ^1H-NMR spectra. The chemical shifts of the two ^{77}Se nuclei (in each compound) are in a typical region to prove that all compounds **3** are unsymmetrical diselenides,[10] although their differences (ca. 177−184 ppm for **3a−c**) are astonishingly large. Moreover, both ^{77}Se resonances of **3a** and **3c** revealed two clearly resolved satellite peaks due to ^{77}Se-^{77}Se coupling in the ^1H-decoupled ^{77}Se-NMR spectra (Figure 1).

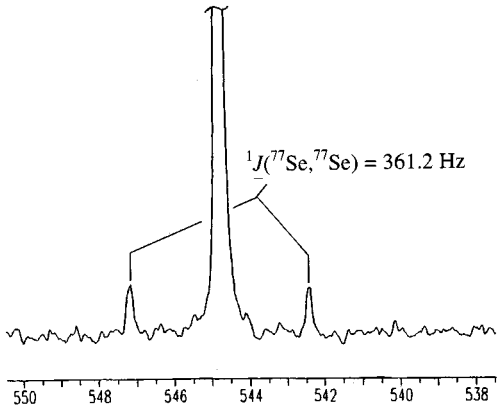

Figure 1. Selection of the ^{77}Se-NMR spectrum of **3a** (Se-8 signal)

These one-bond ^{77}Se-^{77}Se coupling constants (361.2 Hz for **3a** and 360.5 Hz for **3c**) are surprisingly high relative to the few values of neutral diselenides reported in the literature:[10] In neutral diselenides one-bond ^{77}Se-^{77}Se coupling constants range from 2 to 36 Hz. On the other hand, the largest $^1J_{Se,Se}$ value recorded so far was observed in a bicyclic spiroselenoselenide with a double negative charge at the spiro selenium atom ($^1J_{Se,Se} \approx 391$ Hz) and in diselenides with five- and six-membered rings characterized by selenium lone-pair p-orbital overlap, resulting in Se−Se bond-order increase ($^1J_{Se,Se} \approx 374$ Hz).[10][11] A rationalization of the large coupling values is difficult. One may speculate that the reason resides in the planar orientation within the C−Se−Se−C fragment with eclipsed selenium lone pairs leading to a contact between them which is more intimate than in noncyclic diselenides; the latter prefer conformations with torsion angles around the central Se−Se bond of ca 90°.[12]

Compounds with a diselenide link connecting α-carbon atoms of two ketone molecules are described in the literature,[13−16] but an intramolecular diselenide formation by oxidation of α-methylene ketones has not been described before. Therefore, we undertook some attempts to investigate the scope of this reaction, by changing the reaction conditions and the nature of the annulated heterocycles.

At first, we varied the oxidation conditions of the quinazolones **2a−c**. Oxidation without sulfuric acid gave the same diselenides **3a−c**, which, however, were isolated with only half the yields of the reaction in the presence of sulfuric acid. The variation of the ratio of selenious acid to quinazolone from 2:1 to 3:1 did not effect the yields of the products. Oxidation of **2a−c** under different reaction conditions, e.g. by refluxing in dioxane, led to the same results; only diselenides were isolated from reaction mixture after column chromatography. In these cases the yields were again lower than those for oxidation under the original conditions (acetic acid with a catalytic amount of sulfuric acid).

In this context it is interesting to note that the oxidation of 1,6-diphenyl-4,5,6,7-tetrahydro-4-indazolone leads to the corresponding 5-hydroxy-4,7-dihydro-4-indazolone,[2] and it is known that the oxidation of imidazoloquinazolone **4a** provides the corresponding diketone **4b**.[17] To further estimate the influence of the heterocyclic system on the reaction pathway compare the oxidation of two further compounds containing similar structural fragments: the oxidation of the benzacridine derivative **5a**[18] under similar reaction conditions resulted in the α-diketone **5b** with a yield of 95−98%, but the oxidation of 5,5-dimethyl-3,4,5,6-tetrahydro-3-benz[*c*]phenanthridinone **6**[19] gives the diselenide **7**. The structure of this compound and the assignment of the NMR signals in the fragment $-C^4H-Se-Se-C^6H-$ was performed in analogy to **3a−c** and is confirmed by the observation that 6-H is strongly deshielded relative to 8-H in the analogous position of **3a−c** due to the *peri* position of C-7 (Scheme 1).

In summary, a series of compounds belonging to the new bicyclic ring system 2,3-diselenabicyclo[3.2.1]octane have been synthesized. It is not obvious how the aromatic ring(s) annulated to the cyclohexene system can influence the reaction pathways of α-oxidation or diselenide formation. Moreover, the mechanism of the latter reaction remains unknown. Clearly, this reaction deserves further attention.

Experimental Section

The IR spectra were recorded with the Specord 75-IR spectrometer using suspensions of the substances in Nujol (1800−1500 cm^{-1}) and hexachlorobutadiene (3600−2000 cm^{-1}); the frequencies of stretching vibrations of the C−H bonds in the region of 3050−2800 cm^{-1} are not presented. − The NMR spectra of the compounds dissolved in $CDCl_3$ were obtained with a Bruker AM-400 (^1H, 400.1 MHz; ^{13}C, 100.6 MHz; ^{77}Se, 76.3 MHz); Varian Mercury 200BB (^1H, 200 MHz; ^{13}C, 50.3 MHz; ^{77}Se, 38.15 MHz); Bruker AM-360 (^1H, 360 MHz; ^{13}C, 90.5 MHz) spectrometers. The

internal standards were TMS (δ = 0) or HMDS (δ = 0.055) for ^{1}H- and ^{13}C-NMR spectra, and PhSeSePh (external δ = 463). The assignment of ^{1}H, ^{13}C, and ^{77}Se signals was made on the basis of ^{1}H-coupled ^{13}C and HETCOR (^{1}H, ^{13}C) spectra using Bruker and Varian standard packages and by evaluating ^{13}C-^{1}H, ^{77}Se-^{13}C, and ^{77}Se-^{1}H coupling constants. − Mass spectra were recorded with a Finnigan MAT 312. − Elemental analyses were performed with an elemental analyser model 1108 Carlo Erba (Italy). − The syntheses of compounds **2a** and **2c** have been described before.[8][9]

7,7-Dimethyl-2-(3-pyridyl)-5,6,7,8-tetrahydro-5-quinazolone (2b): 3-Amidinopyridine hydrochloride (0.78 g, 5 mmol), 2-formyldimedone (0.84 g, 5 mmol), and piperidine (0.5 mL) as catalyst were refluxed for 5 h in 140 mL of methanol. After 24 h at room temperature, the residue of **2b** was filtered off. The filtrate was concentrated to 2/3 of its volume in a rotary evaporator and then left in the cold for another day. The additional crystals of **2b** were filtered off, and the combined residues were purified by column chromatography (Aeros Silica Gel 35−70 mp with a pore diameter of 6 nm). A mixture of toluene and ethyl acetate (2:1) was used as eluent. − R_f = 0.18. − Yield 0.60 g (47%). − M.p. 106−107°C. − IR: $\tilde{\nu}$ = 1686 cm^{-1}, 1650, 1580, 1550. − ^{1}H NMR ($CDCl_3$): δ = 1.15 (6 H, s, 2 CH_3), 2.59 (2 H, s, 6-H), 3.05 (2 H, s, 8-H), 7.44 (1 H, dd, ^3J = 4.6, 7.3 Hz, 5′-H), 8.74 (2 H, m, 2′-H/6′-H), 9.25 (1 H, s 4-H), 9.68 (1 H, d, ^4J = 1.7, 2′-H). − $C_{15}H_{15}N_3O$ (253.31): calcd. C 71.13, H 5.97, N 16.59; found C 71.01, H 5.92, N 16.52.

2-Aryl-7,7-dimethyl-5,6,7,8-tetrahydro-6,8-epidiseleno-5-quinazolones 3a−c: A mixture of **2a**, **2b**, or **2c** (5 mmol), carefully pounded selenious acid (5 mmol), 10 mL of acetic acid and 0.3 mL of concd. sulfuric acid was left for 72 h at 20°C. Then it was heated to 100°C for 1.5 h and refluxed for 5 to 10 min. The reaction mixture was cooled and selenium was filtered off. The solution was poured onto an ice/ammonia mixture, and the residue was filtered off.

7,7-Dimethyl-2-phenyl-5,6,7,8-tetrahydro-6,8-epidiseleno-5-quinazolones (3a): The reaction product (1.5 g) was purified by column chromatography with CH_2Cl_2 as eluent. − R_f = 0.48. − After removal of the solvent, 0.30 g (36%) of **3a** was obtained. − M.p. 114−116°C. − IR: $\tilde{\nu}$ = 1682 cm^{-1}, 1565, 1545. − ^{1}H NMR ($CDCl_3$): δ = 1.30 (3 H, s, CH_3), 1.48 (3 H, s, CH_3'), 4.18 (1 H, d, ^5J = 0.9 Hz, 6-H), 4.68 (1 H, d, ^5J = 0.9 Hz, 8-H), 7.50 (3 H, m, *meta*- and *para*-phenyl), 8.51 (2 H, m, *ortho*-phenyl), 9.49 (1 H, s, 4-H). − ^{13}C NMR ($CDCl_3$): δ = 21.1 (CH_3, $^1J_{CH}$ = 127.9 Hz), 28.7 (CH_3', $^1J_{CH}$ = 127.9 Hz), 49.9 (C-7), 60.4 (C-8, $^1J_{CH}$ = 150.2 Hz), 62.9 (C-6, $^1J_{CH}$ = 158.6 Hz), 119.2 (C-4a), 128.7 (*ortho*- or *meta*-phenyl, $^1J_{CH}$ = 160.8), 129.1 (*ortho*- or *meta*-phenyl, $^1J_{CH}$ = 160.8), 132.0 (*para*-phenyl, $^1J_{CH}$ = 160.8), 136.6, 158.5 (C-4, $^1J_{CH}$ = 186.6 Hz), 167.7 (C-2), 169.1 (C-8a), 188.7 (C-5). − $C_{16}H_{14}N_2OSe_2$ (408.22): calcd. C 47.09, H 3.46, N 6.86, found, C 46.90, H 3.37, N 6.80.

7,7-Dimethyl-2-(3-pyridyl)-5,6,7,8-tetrahydro-6,8-epidiseleno-5-quinazolones (3b): The yield of unpurified reaction product was 0.60 g. It was chromatographed eluting with a chloroform/ethyl acetate mixture (3:1) and obtained as 0.20 g of residue with 60−70% of **3b**. − R_f = 0.22. − M.p. 115−121 °C. − IR: $\tilde{\nu}$ = 1655 cm^{-1}, 1575, 1560, 1528. − ^{1}H NMR ($CDCl_3$): δ = 1.29 (3 H, s, CH_3), 1.46 (3 H, s, CH_3'), 4.19 (1 H, d, ^5J = 1.0 Hz, 6-H), 4.68 (1 H, d, ^5J = 1.0 Hz, 8-H), ca. 7.45 (1 H, dd, ^3J = 7.7, 6.1 Hz, 5′-H), ca. 8.76 (2 H, m, 2′-H and 6′-H), 9.46 (1 H, s, 4-H), 9.7(1 H, d, ^4J = 2.1 Hz, 2′-H). − ^{13}C NMR ($CDCl_3$): δ = 21.2 (CH_3), 28.8 (CH_3'), 60.2 (C-8), 62.8 (C-6), 123.4 (C-5′), 136.2 (C-4′), 150.5 (C-6′), 152.2 (C-2′), 158.6 (C-4); no signals observed for quaternary C-2, C-4a, C-5, C-7, C-8a, C-3′ due to low signal-to-noise ratio.

7,7-Dimethyl-2-(4-pyridyl)-5,6,7,8-tetrahydro-6,8-epidiseleno-5-quinazolones (3c): This compound was obtained by recrystallization from glacial acetic acid. − Yield 0.75 g (37%). − M.p. 214−215°C. − IR: $\tilde{\nu}$ = 1666 cm^{-1}, 1595, 1570, 1560, 1525. − ^{1}H NMR ($CDCl_3$): δ = 1.30 (3 H, s, CH_3), 1.47 (3 H, s, CH_3'), 4.20 (1 H, d, ^5J = 1.0 Hz, 6-H), 4.69 (1 H, d, ^5J = 1.0 Hz, 8-H), 8.33 (2 H, m, 2′-H/6′-H), 8.83 (2 H, m, 3′-H/5′-H), 9.49 (1 H, s, 4-H). − ^{13}C NMR ($CDCl_3$): δ = 21.1 (CH_3, $^1J_{CH}$ = 127.3 Hz), 28.3 (CH_3', $^1J_{CH}$ = 127.8 Hz), 49.9 (C-7), 60.2 (C-8, $^1J_{CH}$ = 150.7 Hz), 62.8 (C-6, $^1J_{CH}$ = 152.6 Hz), 120.5 (C-4a), 122.4 (C-3′/C-5′, $^1J_{CH}$ = 166.4), 143.7 (C-4′), 150.6 (C-2′/C-6′, $^1J_{CH}$ = 179.3 Hz), 158.8 (C-4, $^1J_{CH}$ = 186.4 Hz), 165.8 (C-2), 169.2 (C-8a), 187.4 (C-5). − EI MS *m/z* (%): 411 (20, 2 ^{80}Se), 251 (100), 236 (36), 223 (39), 222 (22), 208 (31), 197 (9), 160 (11), 119 (29), 105 (21), 91 (21), 78 (26), 77 (27). − HR MS; *m/z*: calcd. 410.9389 for $C_{15}H_{13}N_3O^{80}Se_2$; found 410.9408. − $C_{15}H_{13}N_3OSe_2$ (409.21): calcd. C 44.04, H 3.20, N 10.27; found C 44.86, H 3.26, N 10.23.

9,9-Dimethyl-12-phenyl-8,9,10,11-tetrahydro-10,11-benz[*c*]acridindione (5b): The oxidation of 9,9-dimethyl-12-phenyl-8,9,10,11-tetrahydro-11-benz[*c*]acridinone (**5a**) was carried out by analogy of oxidation of the compounds **2** and **4**. The selenium was filtered off, the solution was poured onto ice and compound **5b** was filtered off. − Yield 90%, 1.64 g. − M.p. 246−247 °C (from ethanol). − IR: $\tilde{\nu}$ = 1725 cm^{-1}, 1690−1680, 1620, 1605, 1560, 1530. − ^{1}H NMR ($CDCl_3$): δ = 1.32 (6 H, s, 2 CH_3), 3.50 (2 H, s, CH_2), 7.05−8.16 (11 H, m, Ar). − $C_{25}H_{19}NO_2$ (365.44): calcd. C 82.17, H 5.24, N 3.83; found C 82.12, H 5.15, N 3.71.

5,5-Dimethyl-3,4,5,6-tetrahydro-4,6-epidiseleno-3-benz[*c*]phenanthridinone (7): This compound was obtained from 5,5-dimethyl-3,4,5,6-tetrahydro-3-benz[*c*]phenanthridinone (0.55 g, 2 mmol) by the method used to synthesize **3a−d** (vide infra). The reaction product was eluted with chloroform. − R_f = 0.43. − 0.31 g (36%) **7** was obtained. − M.p. 238−239°C. − IR: $\tilde{\nu}$ = 1656 cm^{-1}, 1615, 1575, 1560, 1515. − ^{1}H NMR ($CDCl_3$): δ = 1.26 (3 H, s, CH_3), 1.53 (3 H, s, CH_3'), 4.27 (1 H, d, ^5J = 0.7 Hz, 4-H), 5.30 (1 H, d, ^5J = 0.7 Hz, 6-H), 7.7−7.8 and 7.9−8.0 (3 H each, m, Ar), 9.64 (1 H, m, 2-H). − ^{13}C NMR ($CDCl_3$): δ = 20.8 (CH_3), 29.5 (CH_3'), 53.6 (C-6), 62.8 (C-4); 119.4, 125.2, 127.6, 128.9, 129.2, 130.1 (all aromatic CH) 147.9 (C-2), quaternary carbon signals not observed due to low signal-to-noise ratio. − $C_{19}H_{15}NOSe_2$ (431.26): calcd. C 52.93, H 3.51, N 3.25; found C 53.50, H 3.40, N 3.31.

Acknowledgments

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