Derivatives from Isoselenocyanates: Synthesis of 2-Phenyl-6*H*-[5,1,3]benzoselenadiazocine

by **Plamen K. Atanassov**[1]), **Anthony Linden**, and **Heinz Heimgartner***

Organisch-chemisches Institut der Universität Zürich, Winterthurerstrasse 190, CH-8057 Zürich

The reaction of *N*-phenylbenzimidoyl isoselenocyanates **8** with primary and secondary amines in acetone at room temperature, followed by treatment with a base, led to 6*H*-[5,1,3]benzoselenadiazocine derivatives of type **10** (*Scheme 3*). An analogous cyclization was observed when **8a** and **8b** were reacted with the Na salt of diethyl malonate in EtOH at room temperature, which yielded the eight-membered selenaheterocycles **11** (*Scheme 5*). The molecular structures of some of the products, as well as that of a sulfur analogue, have been established by X-ray crystallography (*Figs. 1–4*). The isoselenocyanates **8** have been prepared from *N*-(2-methylphenyl)benzamides **5** in a three-step procedure *via* the corresponding imidoyl chlorides **6**, side-chain chlorination to give **7**, and treatment with KSeCN (*Scheme 2*).

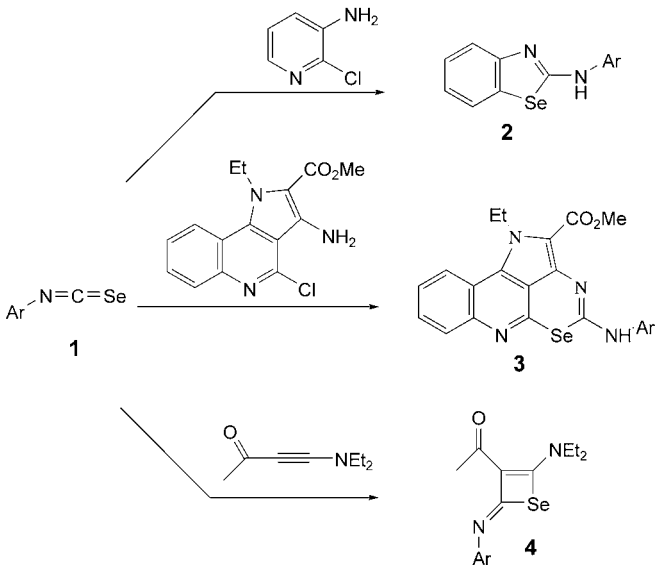
1. Introduction. – The current interest in selenaheterocycles is mainly due to their chemical properties [1–3] and biological functions [4–8] (see also references cited in [9–14]). The main drawbacks of some syntheses are the toxicity of many commonly used Se reagents and the instability of some intermediates. With the aim of developing syntheses of new selenaheterocycles with less-toxic, conveniently accessible, and safely usable Se reagents, we have investigated reactions with various isoselenocyanates. For example, the reaction of aroyl isoselenocyanates with diazoacetate led to 1,2,3-selenadiazoles [9], *N*-arylimidoyl isoselenocyanates were transformed into 2-amino-1,3-selenazoles [10], and *N*-(4-nitrobenzyl)benzimidoyl isoselenocyanates, on treatment with Et_3N, gave bis(2,4-diarylimidazoles-5-yl) diselenides [11]. Recently, we have shown that aryl isoselenocyanates **1** are convenient, cheap, and safe Se reagents for the preparation of selenazolo[5,4-*b*]pyridines **2** [12], 1*H*-[1,3,6]triazaaceanthrylene derivatives **3** [13], and selenet-2(2*H*)-imines **4** [14] (*Scheme 1*).

In this paper, we report the results of the reaction of *N*-phenylbenzimidoyl isoselenocyanates of type **8** with primary and secondary amines, and with the Na salt of diethyl malonate, which leads to eight-membered selenaheterocycles (see [15]). An analogous reaction has been recently used by *Stankovsky* and *Spirkova* to prepare benzothiadiazocines [16].

2. Results and Discussion. – According to a known procedure [17], *N*-[(2-chloromethyl)phenyl]benzimidoyl chloride (**7a**) was prepared from *N*-(2-methylphenyl)benzamide (**5a**) by consecutive treatment in refluxing $SOCl_2$ and with SO_2Cl_2 in boiling benzene in the presence of azobis[isobutyronitrile] (AIBN). To a stirred solution of the crude **7a** in dry acetone, a freshly prepared solution of 1.1 equiv. of

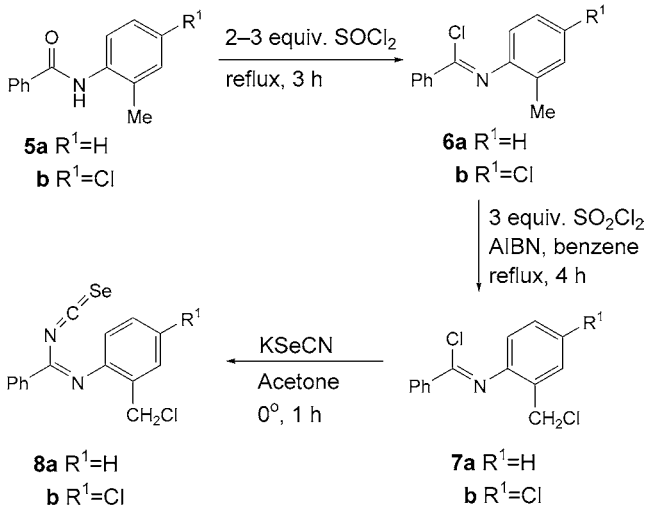
[1]) Part of the Ph.D. thesis of *P. K. A.*, Universität Zürich, 2004.

Scheme 1



KSeCN in dry actone was added at $-5°$ to $0°$, and the mixture was stirred at $0°$ for 1 h. Then, the solvent was evaporated, the residue was dissolved in $CHCl_3$, the solid KCl removed by filtration, and the solvent was evaporated *in vacuo*. The isoselenocyanate **8a** obtained was used for the following reactions without further purification (*Scheme 2*).

Scheme 2



Because of the relatively low yields of the products of the subsequent reactions and the presence of some overchlorinated products (see later), we investigated the formation of **6a** and **7a** in detail. We assumed that the treatment of **5a** with $SOCl_2$ led to partial chlorination of the benzene ring to give a mixture of **6a** and **6b**. Therefore, the product was hydrolyzed and analyzed. According to the elemental analysis, chlorination of the benzene ring occurred under the optimized reaction conditions (3 h) to an extent of 1.5%.

The crude imidoyl chloride **6a** (containing small amounts of **6b**) was dissolved in dry benzene and mixed with 3 equiv. of SO_2Cl_2 and catalytic amounts of AIBN. The mixture was refluxed for 4 h, the solvent and excess SO_2Cl_2 were removed under reduced pressure, the remaining oily product was distilled *in vacuo* (150–170°), and the fractions were analyzed by ^{1}H-NMR. This step has been performed under different conditions, varying the equiv. of SO_2Cl_2 and the reaction time. Under the optimal conditions (3 equiv. of SO_2Cl_2, 4 h), the mixture consisted of *ca.* 13.5% of **6a**/**6b**, *ca.* 72% of **7a**/**7b**, and *ca.* 13.5% of products with a Cl_2CH group. When the reaction was carried out with **6b**, the optimal conditions were 1.5 equiv. of SO_2Cl_2 and 4-h reflux, leading to a mixture of *ca.* 13.5% of the $ClCH_2$ derivative.

The crude isoselenocyanate **8a** was dissolved in acetone, and 0.9 equiv. of morpholine, pyrrolidine, $PhCH_2NH_2$, and cyclohexylamine, respectively, were added while stirring the mixture at room temperature. After 15 min, the precipitate was removed by filtration, and the filtrate was allowed to stand for 24 h. Pale yellow hydrochlorides **9** precipitated (*Scheme 3*). The free bases were obtained after treatment of the hydrochlorides **9** with 1.5–2 equiv. of (diisopropylamino)methyl–polystyrene in $CHCl_3$ at ambient temperature. The remaining oil was triturated with MeOH, and pale yellow crystals of **10** were obtained (*Table 1*). It is important to mention that the reaction failed when excess amine was added at once, or when Et_3N was added before the addition of the primary or secondary amine. In other words, the formation of eight-membered benzoselenadiazocines as HCl salts of type **9** seems to be crucial.

Scheme 3

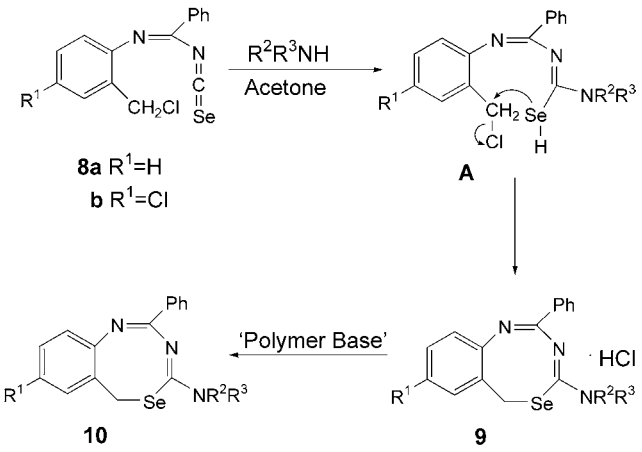


Table 1. *Yields of Benzoselenadiazocines* **10**

Compound	R^1	R^2		R^3	Yield [%][a])
10a	H		$-(CH_2)_2O(CH_2)_2-$		14.4
10b	H		$-(CH_2)_4-$		7.5
10c	H	H		$PhCH_2$	24.1
10d	H	H		Cyclohexyl	14.0
10e	Cl		$-(CH_2)_4-$		7.8

[a]) With respect to crude **7a**.

The structures of the products were established on the basis of their spectroscopic data and elemental analyses, and, in the cases of **10a**, **10c**, and **10d**, X-ray crystal-structure determinations were carried out, confirming the proposed structures.

The crystal structure of **10a** (*Fig. 1*) established the eight-membered 6*H*-[5,1,3]benzoselenadiazocine ring and, therefore, the ring closure between the Se-atom and the CH_2Cl group. The crystal actually proved to be a co-crystal of composition $0.94(C_{19}H_{19}N_3OSe) \cdot 0.06(C_{19}H_{18}ClN_3OSe) \cdot MeOH$. This conclusion was based on the observation that, although the initially developed structural model corresponded with the expected compound **10a**, one peak of residual electron density of 1.9 e A^{-3} remained *ca.* 1.6 Å from C(9) of the phenyl ring. Given the chemical evidence, which indicates that the crystals contain a small amount of a corresponding compound that is Cl-substituted at C(9), the peak was assigned as a partial-occupancy Cl-atom. The site-occupation factor of this Cl-atom was refined to a value of 0.060(2). Therefore, the crystal appears to be a mixture of two compounds: *ca.* 94% is the expected compound **10a**, while *ca.* 6% is the corresponding compound, which is Cl-substituted at C(9). The asymmetric unit in the structure also contains one molecule of MeOH. The OH group of the MeOH molecule forms an intermolecular H-bond with N(5) of the eight-membered ring of the Se compound. This interaction links pairs of **10a** and MeOH together and has a graph set motif [19] of D.

The crystal structures of compounds **10c** and **10d**, obtained from the reaction of **8a** with $PhCH_2NH_2$ and cyclohexylamine, respectively, revealed molecules that are very similar to that of **10a** (*Fig. 2*). There was no evidence for the presence of any *C*(9)-Cl-substituted derivative in either of these structures. In the case of **10c**, there was one significant peak of residual electron density in the region of atoms C(8), C(9), and C(10), but the position of this peak could not be correlated with any chemically sensible atom, so the effect was ignored (see *Exper. Part*). In both structures, the NH group at C(2) forms an intermolecular H-bond with the N(5)-atom of the eight-membered ring of an adjacent molecule. These interactions link the molecules into extended chains, which run parallel to the *x*-axis and *z*-axis, respectively, and have a graph set motif of C(6).

Analogously to the synthesis of **10b**, the Cl derivative **10e** was prepared from **7b**. Treatment with KSeCN gave crude **8b** (*Scheme 2*), which was reacted with pyrrolidine. The hydrochloride **9e** was deprotonated by treatment with polymeric base, and **10e** was obtained in low yield (7.8% with respect to crude **7b**; *Scheme 3*).

For comparison, the analogous reaction was carried out with the benzimidoyl isothiocyanate **11**, which has been described previously [16]. The addition of 0.9 equiv.

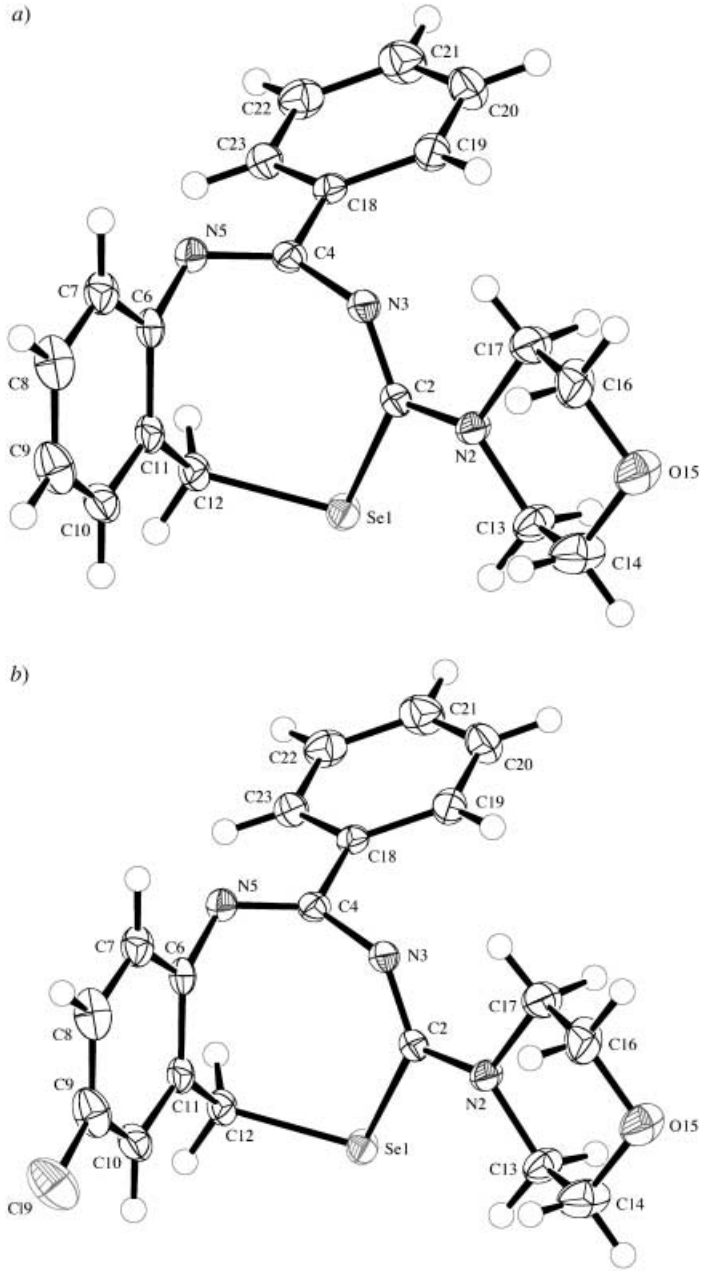


Fig. 1. *ORTEP Plots* [18] *of the molecular structure of* a) **10a** *and* b) *the chlorinated minor product* (50% probability ellipsoids; arbitrary numbering of atoms; the MeOH molecule is not shown)

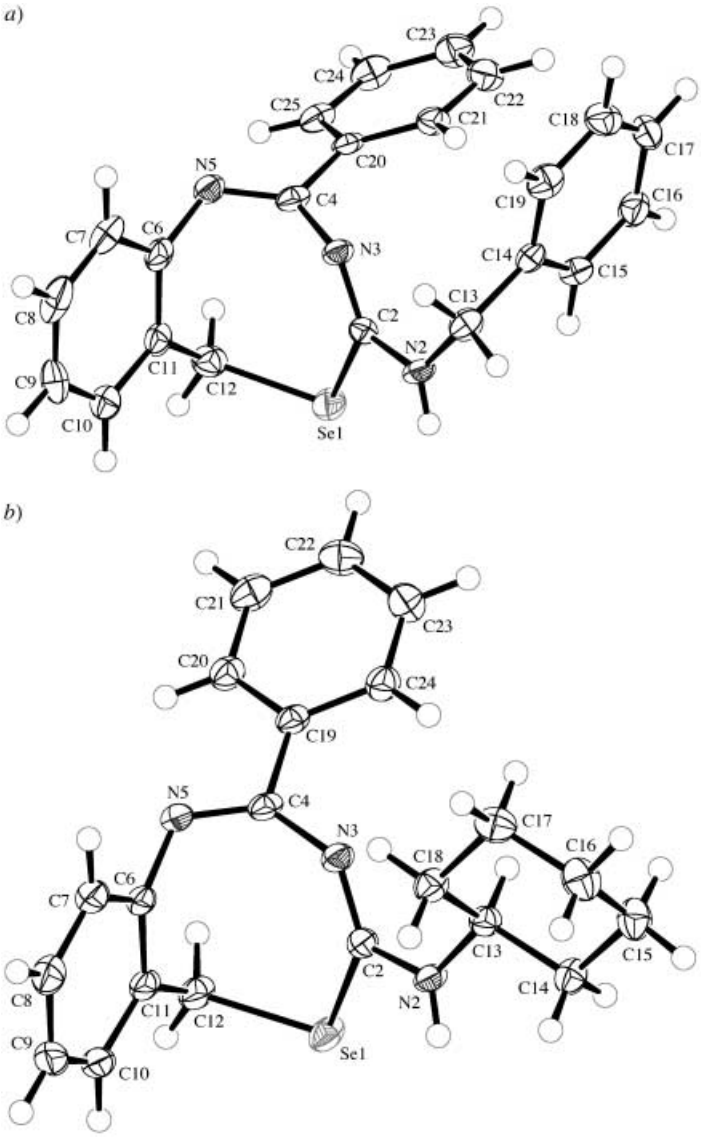
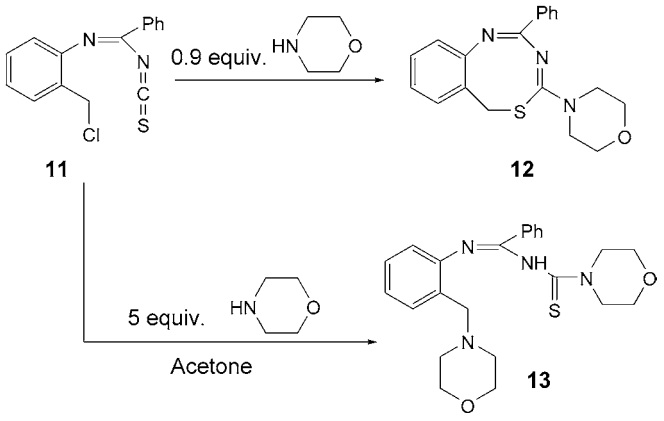


Fig. 2. *ORTEP Plots* [18] *of the molecular structure of* a) **10c** *and* b) **10d** (50% probability ellipsoids; arbitrary numbering of atoms)

of morpholine to a solution of **11** in acetone at room temperature led to the formation of a hydrochloride, which was transformed to the free base **12** (24.6%) by treatment with polymeric base (*Scheme 4*). The structure of **12** was elucidated on the basis of the spectroscopic data and was established by X-ray crystallography (*Fig. 3*). Again, the crystal appeared to be a mixture of two compounds: *ca.* 96% is the expected **12**, while

Scheme 4



ca. 4% is the corresponding compound, which is Cl-substituted at C(9) of the phenyl ring.

When 5 equiv. of morpholine were added at once to the solution of **11** in acetone at room temperature, small amounts (10.6%) of the thiourea derivative **13** were isolated as the only product (*Scheme 4*)[2]). For the formation of this product, two molecules of morpholine have reacted with **11**, *i.e.*, one molecule underwent an addition to the NCS group and the second one a replacement of the Cl-atom of the CH_2Cl group.

In addition to the reactions of **8** with amines as N-nucleophiles, we investigated the corresponding reaction with C-nucleophiles, *e.g.*, the Na salt of diethyl malonate. To a solution of NaOEt in EtOH, diethyl malonate was added at room temperature, followed by **8**. After stirring for 24 h, the solvent was removed, and the residue was dissolved in $CHCl_3$. Filtration and evaporation of the solvent gave an oil, which solidified to give yellow crystals of the eight-membered product **14** (*Scheme 5*). This reaction is analogous to the formation of 5,1,3-benzothiadiazocines from **11** and diethyl malonate [16].

The elemental analyses and CI-MS were in accordance with the expected structure **14′** (analogous to the proposed structure of the S analogue [16]). The IR spectrum showed an intense absorption for C=O at 1711 cm^{-1}, but also a band at 3287 cm^{-1}, which could be assigned to an NH group. This assumption was supported by an NH absorption at 9.61 ppm in the ^{1}H-NMR spectrum. In the ^{13}C-NMR spectrum, the ester CO groups absorb at 156.9 ppm, which indicates extensive conjugation. On the other hand, a signal for a CH group, as in **14′**, was missing. Finally, the structure of **14a** was established by X-ray crystallography (*Fig. 4*).

As with the crystal structure of **10a**, the structure of **14a** revealed the presence of a co-crystal comprising two compounds: *ca.* 96% is **14a**, while *ca.* 4% is the corresponding compound, which is Cl-substituted at C(9) of the phenyl ring. The NH group of the molecule forms an intermolecular H-bond with the C=O O-atom of one of the ester

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[2]) In the case of the Se analogue **8**, no analogous product could be observed when excess morpholine was used, and only extensive decomposition occurred.

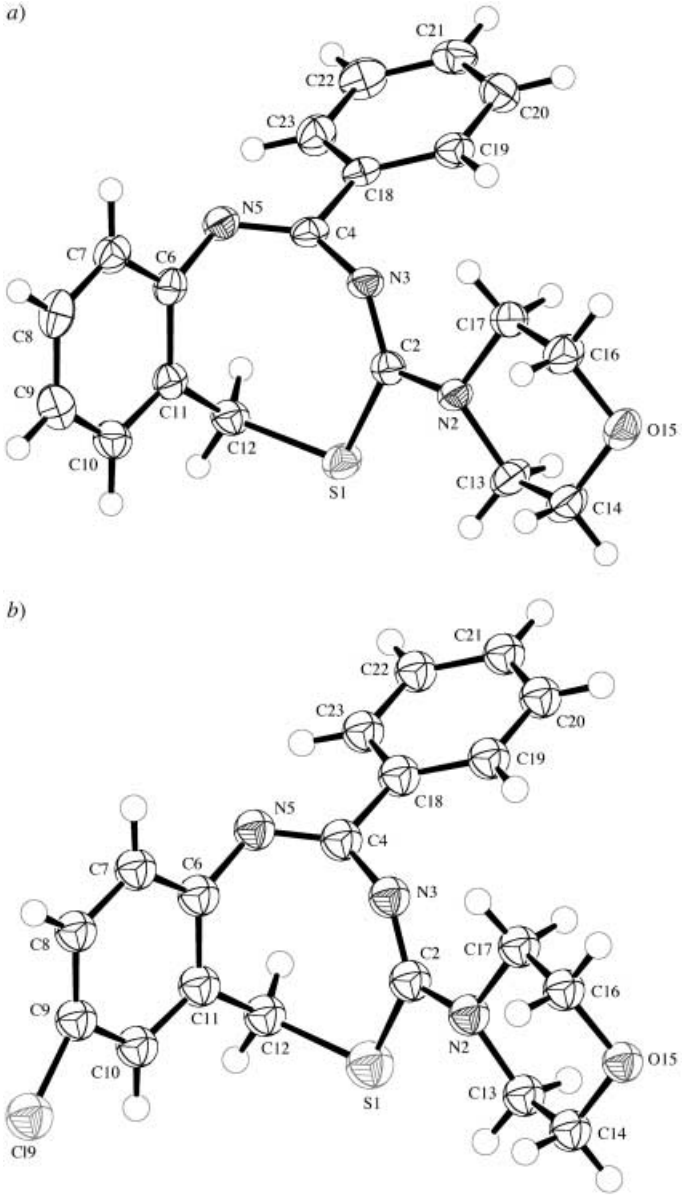
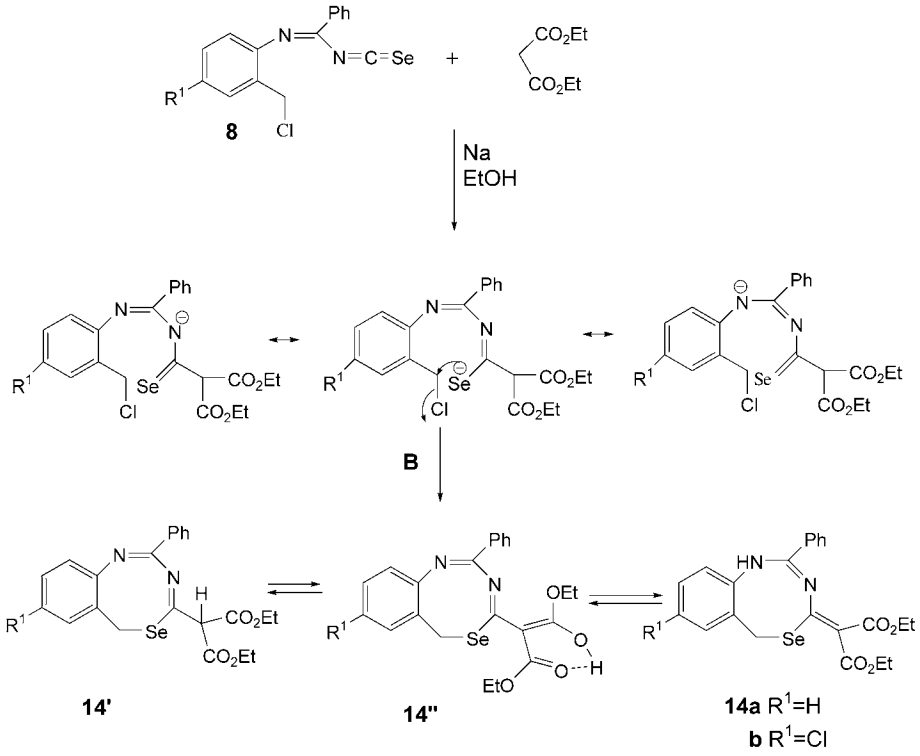


Fig. 3. *ORTEP Plots* [18] *of the molecular structure of* a) **12** *and* b) *the chlorinated minor product* (50% probability ellipsoids; arbitrary numbering of atoms)

groups of a neighboring molecule. These interactions link the molecules into extended chains, which run parallel to the *z*-axis and have a graph set motif of C(8).

In conclusion, we have shown that *N*-phenylbenzimidoyl isoselenocyanates react with amines and C-nucleophiles to give 6*H*-[5,1,3]benzoselenadiazocines *via* a

Scheme 5



nucleophilic addition to the heterocumulene moiety followed by cyclization. The yields of the eight-membered products are only modest, mainly because of the difficulty of preparing the starting *N*-[2-(chloromethyl)phenyl]benzimidoyl chloride selectively.

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Experimental Part

1. *General*. See [9]. IR Spectra in KBr; ^{1}H- and ^{13}C-NMR spectra in $CDCl_3$ unless otherwise stated.

2. *Preparation of* N-*Phenylbenzamides. General Procedure*. To a cooled soln. of *o*-toluidine (0.075 mol) in pyridine (60 ml, ice bath), PhCOCl (10.96 g, 0.078 mol) was added slowly under stirring. After 10 min, the ice-bath was removed, and the mixture was stirred for 3 h at r.t. Then, cold H_2O (200 ml) was added, and the mixture was stirred at 0° for 10 min. The solid material was filtered and washed several times with cold H_2O. The crude product was recrystallized from EtOH.

N-*(2-Methylphenyl)benzamide* (**5a**). From 8.00 g (75 mmol) of *o*-toluidine and 10.96 g (78 mmol) PhCOCl: 12.3 g (78%). White crystals. M.p. 144.0–145.0° (EtOH). ^{1}H-NMR: 8.00–7.70, 7.60–7.40, 7.30–7.00 (3*m*, 9 arom. H, NH); 2.28 (*s*, Me).

N-*(4-Chloro-2-methylphenyl)benzamide* (**5b**). From 10.62 g (75 mmol) of 4-chloro-2-methylaniline and 10.96 g (78 mmol) PhCOCl: 15.54 g (84.4%). White crystals. M.p. 173.0–173.9° (EtOH). ^{1}H-NMR: 8.00–7.70, 7.60–7.40, 7.20–7.00 (3*m*, 8 arom. H); 7.61 (*s*, NH); 2.21 (*s*, Me).

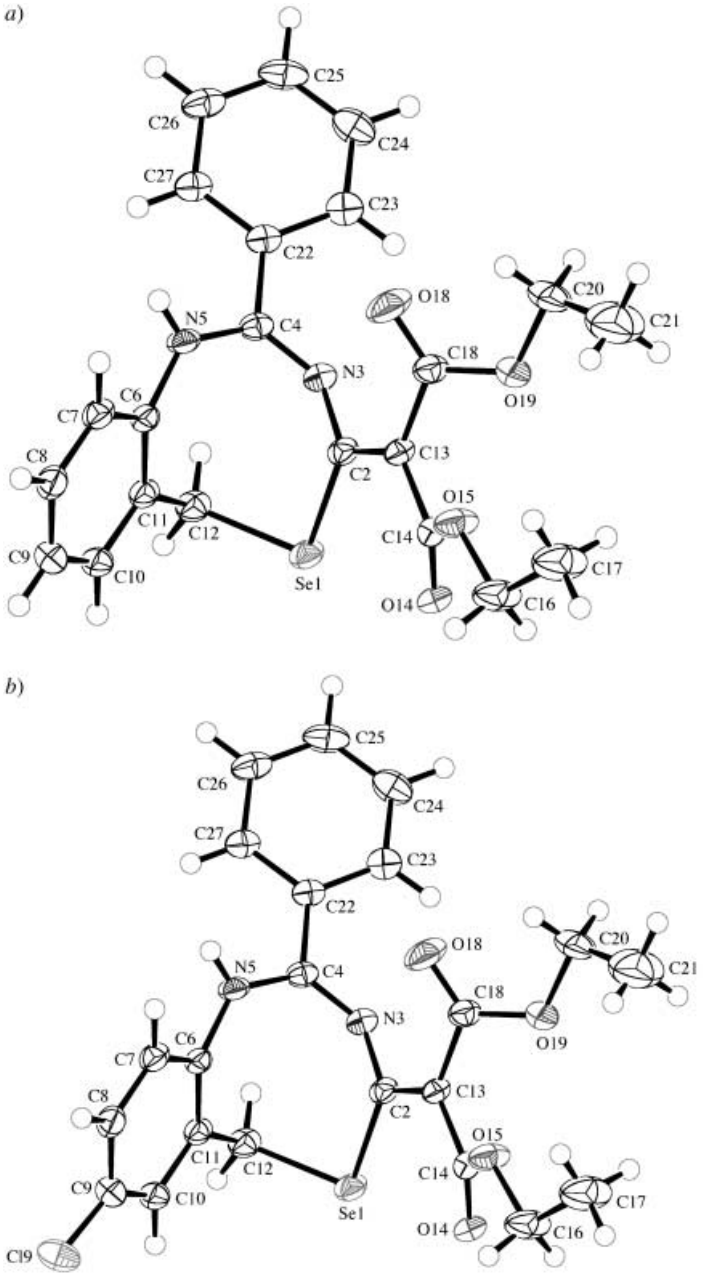

Fig. 4. *ORTEP Plots* [18] *of the molecular structure of* a) **14a** *and* b) *the chlorinated minor product* (50% probability ellipsoids; arbitrary numbering of atoms)

3. *Preparation of* N-*[2-(Chloromethyl)phenyl]benzimidoyl Chlorides.* A mixture of **5** and 2–3 equiv. of $SOCl_2$ was heated to reflux until the evolution of SO_2 ceased (3 h). The excess $SOCl_2$ was removed *i.v.* The crude, oily imidoyl chloride **6** was dissolved in dry benzene, mixed with 3 equiv. of SO_2Cl_2 and a cat. amount of azobis[isobutyronitrile] (AIBN), and the mixture was refluxed for 4 h. The solvent and excess SO_2Cl_2 were removed under reduced pressure, the remaining oily product was purified by distillation *i.v.* (b.p. 150–170°/0.041 Torr), and the fractions were analyzed by ^{1}H-NMR spectroscopy. Chlorination at C(4) of the benzene ring connected to the N-atom was observed. According to the elemental analysis of the hydrolyzed product of **6a**, *ca.* 1.5% of the chlorinated product was present.

N-*[2-(Chloromethyl)phenyl]benzimidoyl Chloride* (**7a**): ^{1}H-NMR: 8.20–7.00 (*m*, 9 arom. H); 4.53 (*s*, CH_2Cl of **7a**); 4.46 (*s*, CH_2Cl of **7b**); 2.25 (*s*, Me of **6b**); 2.15 (*s*, Me of **6a**). ^{13}C-NMR: 146.3–120.2 (arom. C, C=N); 67.9, 66.9 (2*d*, $CHCl_2$); 42.9, 42.7 (2*t*, CH_2Cl of **7b** and **7a**); 17.7, 16.7 (2*q*, Me of **6a** and **6b**).

N-*[4-Chloro-2-(chloromethyl)phenyl]benzimidoyl Chloride* (**7b**): ^{1}H-NMR: 8.17–6.89 (*m*, 8 arom. H); 4.44 (*s*, CH_2Cl); 2.11 (*s*, Me of **6b**). ^{13}C-NMR: 145.7–121.6 (arom. C, C=N); 66.9 (*d*, $CHCl_2$); 42.0 (*t*, CH_2Cl); 17.7 (*q*, Me of **6b**).

4. *Preparation of 4-Amino-2-phenyl-6*H-*[5,1,3]benzodiazocines. General Procedure.* A freshly prepared soln. of 1.1 equiv. of KSeCN in dry acetone was added to a stirred soln. of **7** in dry acetone at −5° to 0°. The stirring was continued at 0° for 1 h, and the solvent was removed *i.v.* $CHCl_3$ was added to the residue, the precipitated KCl was removed by filtration, the solvent was removed *i.v.*, and the remaining oily isoselenocyanate **8** was used without additional purification. When 0.9 equiv. of the corresponding amine were added slowly (15 min) to a stirred soln. of the crude **8** in acetone at r.t., the yellow color of the soln. changed to dark brown. The mixture was stirred for another 15 min, while the formation of amine·HCl was observed. This salt was removed by filtration, and the filtrate was left to stand at r.t. for 24 h. Pale yellow **9** precipitated, the soln. was decanted, the residue was dissolved in $CHCl_3$, 1.5–2 equiv. of (diisopropylamino)methyl–polystyrol (polymer base) were added, and the mixture was stirred for 10 min. The polymer base was filtered, the solvent was removed *i.v.*, and the remaining oil was dissolved in MeOH. Pale yellow crystals of **10** were formed, which were recrystallized from MeOH.

*4-(Morpholin-4-yl)-2-phenyl-6*H-*[5,1,3]benzoselenadiazocine* (**10a**). From 1 g (3.78 mmol) of **7a** and 296.4 mg (3.40 mmol) of morpholine: 0.2 g (14.4%). Yellowish crystals. M.p. 120.9–121.9° (MeOH). IR: 3409*w*, 3062*w*, 3020*w*, 2957*m*, 2923*w*, 2896*m*, 2847*s*, 1688*w*, 1630*s*, 1587*s*, 1567*s*, 1488*m*, 1478*s*, 1445*s*, 1427*m*, 1367*s*, 1357*s*, 1309*m*, 1287*m*, 1275*m*, 1263*s*, 1236*m*, 1202*s*, 1190*s*, 1169*s*, 1139*m*, 1115*s*, 1088*m*, 1058*s*, 1010*s*. ^{1}H-NMR: 8.10–6.80 (*m*, 9 arom. H); 4.50 (*d*-like, 1 H of CH_2Se); 3.58–3.35 (*m*, 4 CH_2 of morpholine, 1 H of CH_2Se). ^{13}C-NMR: 160.1, 148.0, 134.0, 129.9 (4*s*, 2 C=N, 3 arom. C); 131.1, 128.6, 128.3, 128.7, 124.0, 121.1 (6*d*, 9 arom. CH); 66.2 (*t*, 2 CH_2O); 49.0 (*t*, 2 CH_2N); 27.2 (*t*, CH_2Se). CI-MS: 386 (100, $[M+1]^+$), 274 (15).

*2-Phenyl-4-(pyrrolidin-1-yl)-6*H-*[5,1,3]benzoselenadiazocine* (**10b**). From 1 g (3.78 mmol) of **7a** and 241.8 mg (3.40 mmol) of pyrrolidine: 0.1 g (7.5%). Yellowish crystals. M.p. 166.0–167.0° (MeOH). IR: 3431*w*, 3060*w*, 2967*w*, 2922*w*, 2862*w*, 1616*s*, 1584*s*, 1564*s*, 1473*m*, 1446*m*, 1421*w*, 1383*s*, 1335*s*, 1276*w*, 1264*s*, 1225*s*, 1186*m*, 1168*s*, 1137*m*, 1088*m*, 1052*s*, 1033*m*, 1022*m*. ^{1}H-NMR: 8.10–6.80 (*m*, 9 arom. H); 4.55 (*d*-like, 1 H of CH_2Se); 3.48–3.15 (*m*, 2 CH_2N of pyrrolidine, 1 H of CH_2Se); 1.76 (*t*-like, 2 CH_2 of pyrrolidine). ^{13}C-NMR: 159.3, 150.9, 143.6, 136.7, 129.8 (5*s*, 2 C=N, 3 arom. C); 130.3, 128.6, 128.4, 128.2, 128.0, 123.3, 121.0 (7*d*, 9 arom. CH); 49.2 (*t*, 2 CH_2N of pyrrolidine); 27.0 (*t*, 2 CH_2 of pyrrolidine); 25.0 (*t*, CH_2Se). CI-MS: 370 (100, $[M+1]^+$), 368 (55), 366 (24). Anal. calc. for $C_{19}H_{19}N_3Se$ (368.33): C 61.96, H 5.20, N 11.41; found: C 61.76, H 5.19, N 11.68.

*4-(Benzylamino)-2-phenyl-6*H-*[5,1,3]benzoselenadiazocine* (**10c**). From 2 g (7.5 mmol) of **7a** and 723.3 mg (6.75 mmol) of $PhCH_2NH_2$: 0.7 g (24.1%). Yellowish crystals. M.p. 162.1–163.0° (toluene). IR: 3220*m*, 3059*w*, 3026*w*, 2990*w*, 2937*w*, 1634*s*, 1584*s*, 1563*s*, 1507*s*, 1493*s*, 1477*s*, 1450*m*, 1429*m*, 1359*m*, 1327*s*, 1305*m*, 1277*w*, 1247*m*, 1216*s*, 1172*m*, 1138*w*, 1093*m*, 1067*m*. ^{1}H-NMR: 7.97–7.93 (*m*, 2 arom. H); 7.48–6.90 (*m*, 12 arom. H); 5.00 (br. *s*, NH); 4.66 (*d*, $^2J = 10.5$, 1 H of CH_2Se); 4.53 (*dd*, $J = 15.1$, 6.2, 1 H of $PhCH_2$); 4.19 (*dd*, $J = 15.1$, 4.0, 1 H of $PhCH_2$); 3.51 (*d*, $^2J = 10.5$, 1 H of CH_2Se). ^{13}C-NMR: 160.8, 143.0, 135.8, 137.8, 130.2 (5*s*, 2 C=N, 4 arom. C); 130.7, 128.9, 128.7, 128.5, 128.4, 128.2, 127.2, 123.5, 120.9 (9*d*, 14 arom. CH); 47.0 (*t*, $PhCH_2$); 27.0 (*t*, CH_2Se). CI-MS: 406 (100, $[M+1]^+$). Anal. calc. for $C_{22}H_{19}N_3Se$ (404.37): C 65.35, H 4.74, N 10.39; found: C 65.09, H 4.78, N 10.22.

*4-(Cyclohexylamino)-2-phenyl-6*H-*[5,1,3]benzoselenadiazocine* (**10d**). From 1 g (3.78 mmol) of **7a** and 337.2 mg (3.40 mmol) of cyclohexylamine: 0.2 g (14.0%). Yellowish crystals. M.p. 135–136° (toluene). IR: 3147*m*, 3060*w*, 2928*s*, 2853*s*, 1629*s*, 1583*s*, 1551*s*, 1527*s*, 1478*s*, 1445*s*, 1424*m*, 1356*s*, 1250*m*, 1207*s*, 1180*m*, 1170*m*, 1147*w*. ^{1}H-NMR: 8.05–8.02 (*m*, 2 arom. H); 7.48–6.94 (*m*, 7 arom. H); 4.62 (*d*, $^2J = 10.3$, 1 H of CH_2Se); 4.50 (*d*-like, NHC_6H_{11}); 3.52–3.48 (*m*, 1 H of CH_2Se, 1 H of C_6H_{11}); 1.94–0.70 (*m*, 10 H of C_6H_{11}). ^{13}C-NMR: 161.1, 141.4, 136.1, 130.6 (4*s*, 2 C=N, 3 arom. C); 130.5, 128.7, 128.5, 128.4, 128.2, 123.2, 120.6 (7*d*, 9 arom. CH); 52.0

(*d*, CH of C_6H_{11}); 32.3, 31.8, 27.0, 25.5, 24.5, 24.3 (6*t*, 5 CH_2 of C_6H_{11}, CH_2Se). CI-MS: 398 (100, $[M+1]^+$). Anal. calc. for $C_{21}H_{23}N_3Se$ (396.39): C 63.63, H 5.85, N 10.60; found: 63.61, 5.67, 10.43.

*8-Chloro-2-phenyl-4-(pyrrolidin-1-yl)-6*H*-[5,1,3]benzoselenadiazocine* (**10e**). From 1 g (3.35 mmol) of **7b** and 214.4 mg (3.02 mmol) of pyrrolidine: 0.1 g (7.8%). Yellowish crystals. M.p. 176.0–176.1° (MeOH). IR: 3425*w*, 3058*w*, 2987*w*, 2948*w*, 2865*m*, 1610*s*, 1597*s*, 1581*s*, 1567*s*, 1488*w*, 1466*s*, 1424*m*, 1392*s*, 1332*s*, 1307*m*, 1270*s*, 1258*m*, 1229*s*, 1181*s*, 1162*s*, 1131*m*, 1099*m*, 1077*m*. ^{1}H-NMR: 8.10–6.80 (*m*, 8 arom. H); 4.50 (*d*-like, 1 H of CH_2Se); 3.56–3.07 (*m*, 2 CH_2N of pyrrolidine, 1 H of CH_2Se); 1.79 (*t*-like, 2 CH_2 of pyrrolidine). CI-MS: 404 (100, $[M+1]^+$), 402 (50). Anal. calc. for $C_{19}H_{18}ClN_3Se$ (402.78): C 56.66, H 4.50, N 10.43; found: C 56.40, H 4.65, N 10.51.

5. *Reactions with* N*-[2-(Chloromethyl)phenyl]benzimidoyl Isothiocyanate* (**8**). A soln. of **7a** (1.0 g, 3.78 mmol) in dry acetone (6 ml) was stirred at 0°, while a soln. of KSCN (0.39 g, 4 mmol) in dry acetone (20 ml) was added dropwise. The stirring was continued at 0° for 1 h. The solvent was removed *i.v.*, and $CHCl_3$ (35 ml) was added to the residue. The precipitated KCl was removed by filtration, the solvent was evaporated *i.v.*, and the remaining isothiocyanate **8** was used without further purification. It was dissolved in 25 ml of dry acetone, morpholine (1.65 g, 5 equiv.) was added at once, and the mixture was stirred for 15 min at r.t. Then, the reaction was quenched with H_2O, the mixture was extracted with CH_2Cl_2 (3×), and the extracts were combined and evaporated to dryness. The remaining glue was purified by flash chromatography (AcOEt/hexane 1:2.5) and crystallization from the same solvent mixture. Yield: 0.17 g (10.6%) of **13**. Yellowish crystals. M.p. 183.9–184.8° (AcOEt/hexane). IR: 3443*w*, 3230*m*, 3060*w*, 2971*m*, 2949*s*, 2907*s*, 2875*s*, 2843*s*, 2826*s*, 1675*s*, 1587*s*, 1576*s*, 1530*s*, 1494*m*, 1474*s*, 1453*s*, 1427*s*, 1362*m*, 1346*s*, 1315*s*, 1298*s*, 1287*s*, 1259*s*, 1239*s*, 1222*s*, 1208*s*, 1180*m*, 1157*w*, 1114*s*, 1081*s*, 1069*m*, 1044*w*, 1027*s*, 1005*s*. ^{1}H-NMR: 10.88 (*s*, NH); 7.90–6.80 (*m*, 9 arom. H); 4.13 (*t*-like, CH_2O); 3.89 (*t*-like, CH_2O); 3.69 (*t*-like, CH_2O); 3.64 (*t*-like, CH_2O); 3.62 (*t*-like, CH_2N); 3.55–3.51 (*m*, CH_2N, CH_2Ar); 2.36 (*t*-like, 2 CH_2N). ^{13}C-NMR: 188.8 (*s*, CS); 155.9, 139.4, 135.2, 126.4 (4*s*, C=N, 3 arom. C); 130.8, 130.2, 128.4, 128.1, 123.6, 122.0 (6*d*, 9 arom. CH); 66.6, 66.3, 62.0 (3*t*, 4 CH_2O); 53.0, 48.6 (2*t*, 4 CH_2N); 47.8 (*t*, ArCH_2). ESI-MS: 425 (70, $[M+1]^+$), 338 (84), 279 (100). Anal. calc. for $C_{23}H_{28}N_4O_2S$ (424.56): C 65.07, H 6.65, N 13.20; found: C 65.07, H 6.82, N 13.07.

*4-(Morpholin-4-yl)-2-phenyl-6*H*-[5,1,3]benzothiadiazocine* (**12**). From 1 g (3.78 mmol) of **7a** and 296.4 mg (3.40 mmol) of morpholine: 0.3 g (24.6%). Yellowish crystals. M.p. 136–137° (MeOH). IR: 3424*w*, 3059*w*, 3025*w*, 2984*w*, 2971*m*, 2956*w*, 2931*w*, 2913*w*, 2890*w*, 2855*m*, 2843*m*, 1622*s*, 1587*s*, 1564*s*, 1477*s*, 1448*s*, 1362*s*, 1352*s*, 1301*m*, 1288*m*, 1265*s*, 1251*m*, 1236*m*, 1198*s*, 1184*s*, 1169*s*, 1122*s*, 1096*s*, 1060*s*, 1032*s*, 1024*m*, 1033*s*. ^{1}H-NMR ((D_6)DMSO): 8.10–6.80 (*m*, 9 arom. H); 4.22 (*d*-like, 1 H of CH_2S); 3.78 (*d*-like, 1 H of CH_2S); 3.45 (narrow *m*, 4 CH_2 of morpholine). ^{13}C-NMR (D_6)DMSO): 158.6, 151.6, 150.9, 135.9, 127.4 (5*s*, 2 C=N, 3 arom. C); 130.6, 129.1, 128.5, 128.2, 127.7, 123.4, 120.6 (7*d*, 9 arom. CH); 65.5 (*t*, 2 CH_2O); 47.3 (*t*, 2 CH_2N); 31.9 (*t*, CH_2S). CI-MS: 338 (100, $[M+1]^+$), 226 (8).

6. *Preparation of Diethyl 2-(1*H*,6*H*-[5,1,3]Benzoselenadiazocin-4-ylidene)propanedioates.* To a soln. of EtONa, prepared from Na (0.1 g, 4.34 mmol) and abs. EtOH (3 ml), 0.7 g (4.37 mmol) of diethyl propanedioate was added. The mixture was stirred at r.t. until the Na was completely dissolved. Then, the oily isoselenocyanate **8** and additional abs. EtOH (20 ml) was added, providing an orange-yellow-colored mixture. A small amount of CH_2Cl_2 was added to dissolve **8** completely, and the mixture was stirred at r.t. for 24 h. The solvent was removed *i.v.*, $CHCl_3$ was added to the residue, and the precipitated NaCl was removed by filtration. The solvent was removed *i.v.*, the remaining oil was dissolved in MeOH, and yellow crystals of **14** were formed.

*Diethyl 2-(2-Phenyl-1*H*,6*H*-[5,1,3]benzoselenadiazocin-4-ylidene)propanedioate* (**14a**). From 1.0 g (3.78 mmol) of **7a**: 0.5 g (27.5%). Yellowish crystals. M.p. 179.4–180.4° (MeOH). IR: 3287*m*, 3119*w*, 3059*w*, 2979*w*, 2940*w*, 1711*s*, 1634*s*, 1601*s*, 1585*s*, 1540*s*, 1447*m*, 1431*m*, 1385*w*, 1363*m*, 1330*s*, 1273*s*, 1242*s*, 1187*s*, 1095*s*, 1054*s*, 1027*m*. ^{1}H-NMR ((D_6)DMSO): 9.61 (*s*, NH); 8.00–6.90 (*m*, 9 arom. H); 4.15–3.75 (*m*, 3 CH_2); 1.09 (*t*, $J=7.1$, 2 Me). ^{13}C-NMR ((D_6)DMSO): 156.9 (*s*, 2 CO); 147.6, 135.4, 134.8, 134.7 (4*s*, 3 C, 3 arom. C); 131.2, 130.2, 128.6, 128.2, 126.7, 126.2, 123.2 (7*d*, 9 arom. CH); 59.6 (*t*, 2 CH_2O); 25.3 (*t*, CH_2Se); 13.9 (*q*, 2 Me). CI-MS: 459 (100, $[M+1]^+$). Anal. calc. for $C_{22}H_{22}N_2O_4Se$ (457.38): C 57.77, H 4.85, N 6.12; found: C 57.51, H 4.78, N 6.08.

*Diethyl 2-(8-Chloro-2-phenyl-1*H*,6*H*-[5,1,3]benzoselenadiazocin-4-ylidene)propanedioate* (**14b**). From 1.0 g (3.35 mmol) of **7b**: 0.3 g (17.5%). Yellowish crystals. M.p. 192.5–193.5° (MeCN). IR: 3295*s*, 3109*w*, 3056*w*, 2979*m*, 2942*w*, 2905*w*, 2870*w*, 1709*s*, 1636*s*, 1596*m*, 1583*m*, 1533*s*, 1488*s*, 1448*m*, 1429*m*, 1394*w*, 1385*w*, 1364*s*, 1332*s*, 1275*s*, 1242*s*, 1183*s*, 1095*s*, 1071*m*, 1047*s*, 1028*s*. ^{1}H-NMR ((D_6)DMSO): 9.78 (*s*, NH); 7.83–7.15 (*m*, 8 arom. H); 4.03–3.95 (*m*, 3 CH_2); 1.09 (*t*, $J=7.1$, 2 Me). ^{13}C-NMR ((D_6)DMSO): 156.4 (*s*, CO); 147.7, 137.6, 134.6, 133.8, 129.5, 109.3 (6*s*, 3 C, 4 arom. C); 131.3, 129.5, 128.7, 128.2, 126.7, 125.0 (6*d*, 8 arom. CH); 59.8 (*t*, 2 CH_2O); 24.9 (*t*, CH_2Se); 13.8 (*q*, 2 Me). CI-MS: 493 (100, $[M+1]^+$), 491 (55).

Table 2. *Crystallographic Data of* **10a**, **10c**, **10d**, **12**, *and* **14a**

	10a	**10c**	**10d**	**12**	**14a**
Crystallized from	MeOH	MeOH	MeOH	MeOH	benzene
Empirical formula	$C_{19}H_{18.94}Cl_{0.06}N_3OSe \cdot CH_3OH$	$C_{22}H_{19}N_3Se$	$C_{21}H_{23}N_3Se$	$C_{19}H_{18.96}Cl_{0.04}N_3OS$	$C_{22}H_{21.96}Cl_{0.04}N_2O_4Se$
Formula weight [g mol^{-1}]	419.39	404.31	396.33	338.92	458.67
Crystal color, habit	colorless, prism	colorless, needle	pale yellow, plate	colorless, prism	colorless, needle
Crystal dimensions [mm]	$0.15 \times 0.25 \times 0.30$	$0.05 \times 0.10 \times 0.20$	$0.07 \times 0.17 \times 0.20$	$0.08 \times 0.12 \times 0.22$	$0.10 \times 0.12 \times 0.30$
Temp. [K]	273(1)	160(1)	160(1)	160(1)	160(1)
Crystal system	triclinic	monoclinic	monoclinic	monoclinic	monoclinic
Space group	$P\bar{1}$	$P2_1/c$	$P2_1/c$	$P2_1/c$	$P2_1/c$
Z	2	4	4	4	4
Reflections for cell determination	19631	59768	38430	3909	34266
2θ Range for cell determination [°]	4 – 60	4 – 60	4 – 60	2 – 55	2 – 60
Unit-cell parameters a [Å]	8.8121(1)	7.2795(1)	16.1257(2)	8.5473(1)	15.8889(2)
b [Å]	10.5147(1)	23.9734(3)	8.6671(1)	22.8421(4)	8.4845(1)
c [Å]	11.2697(1)	10.3480(1)	13.3571(1)	9.1539(1)	15.7701(2)
α [°]	80.8246(6)	90	90	90	90
β [°]	71.8921(6)	92.1258(5)	91.4886(5)	110.9784(9)	106.6631(7)
γ [°]	79.0644(5)	90	90	90	90
V [Å^3]	968.81(2)	1804.63(4)	1866.20(3)	1668.73(4)	2036.68(4)
D_x [g cm^{-3}]	1.434	1.488	1.411	1.349	1.496
$\mu(\mathrm{Mo}K_\alpha)$ [mm^{-1}]	1.964	2.090	2.019	0.212	1.879
Scan type	ϕ and ω	ϕ and ω	ϕ and ω	ϕ and ω	ϕ and ω
$2\theta_{(\max)}$ [°]	60	60	60	55	60
Transmission factors (min; max)	0.608; 0.759	0.687; 0.881	0.638; 0.833	–	0.645; 0.823
Total reflections measured	31912	42906	55731	37406	54315
Symmetry independent reflections	5637	5275	5448	3799	5952
Reflections used [$I > 2\sigma(I)$]	5084	4346	4675	2713	4608
Parameters refined	249	239	230	227	276
Final R	0.0297	0.0478	0.0296	0.0425	0.0369
wR	0.0319	0.0491	0.0322	0.0415	0.0378
Weights: p in $w = [\sigma^2(F_O) + (pF_O)^2]^{-1}$	0.005	0.005	0.005	0.01	0.01
Goodness-of-fit	2.142	3.047	2.297	2.006	1.860
Secondary extinction coefficient	$1.1(2) \times 10^{-6}$	–	–	$7(2) \times 10^{-7}$	$2.6(8) \times 10^{-7}$
Final $\Delta_{\max}/\sigma$	0.001	0.0006	0.001	0.0004	0.0008
$\Delta\rho$ (max; min) [e Å^{-3}]	0.34; −0.45	1.83; −0.91	0.46; −0.52	0.31; −0.27	0.44; −0.54

7. *X-Ray Crystal-Structure Determination of* **10a**, **10c**, **10d**, **12**, *and* **14a** (see *Table 2* and *Figs. 1–4*)[3]. All measurements were performed at 160 K (273 K in the case of **10a**) on a *Nonius Kappa CCD* diffractometer [20] with graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. The data collection and refinement parameters are given in *Table 2*, and views of the molecules are shown in *Figs. 1–4*. Data reduction was performed with *HKL Denzo* and *Scalepack* [21]. The intensities were corrected for *Lorentz* and polarization effects, and a numerical absorption correction [22] was applied in the cases of **10a**, **10c**, **10d**, and **14a**. Each structure was solved by direct methods with SIR92 [23], which revealed the positions of all non-H-atoms.

After the initial structural model for **10a**, **12**, and **14a** had been refined, a residual electron-density peak of 1.9, 0.9, and 1.4 e A^{-3}, respectively, remained *ca.* 1.6 Å from C(9) of the phenyl ring. Given the chemical evidence, which suggests this peak could be due to the presence of a small amount of a Cl-substituted derivative, a low-occupancy Cl-atom was defined at the site of the residual peak and the *R* factors subsequently improved significantly. Refinement of the site-occupation factor yielded a value of 0.060(2), 0.043(2), and 0.039(2), respectively, while the anisotropic atomic-displacement parameters remained reasonable. Thus, it is assumed that a Cl-substituent exists at C(9) in *ca.* 6, 4, and 4%, respectively, of the molecules in the crystals, so that the crystals are mixtures of two compounds sharing the same position in the unit cell, hence having the appearance of disorder, and this assumption was employed in defining the final refinement model. The geometry involving the C(9)–Cl(9) bond is quite poor in each structure, for example C(9)–Cl(1) in **10a** is 1.57 Å instead of the usual 1.76 Å, but this is not surprising given that the low site occupation of the Cl-atom results in low precision for the position of this atom, and the fact that, in the model, this Cl-atom is disordered and partially overlapping with the H-atom at C(9) in the unsubstituted major component. In the case of **10a**, the asymmetric unit also contains one molecule of MeOH.

For **10c**, after the structural model corresponding to the expected molecule had been defined and refined fully, one peak of residual electron density of 1.8 e $Å^{-3}$ also remained. This peak is positioned over the outer end of the benzyl ring, but to the side of the ring. The peak is 1.24, 0.92, and 1.61 Å from atoms C(8), C(9), and C(10), respectively. This peak cannot be reconciled with any obvious chemical explanation as it is not possible for a substituent on the ring to adopt this position, so the peak was ignored in the final refinement. The next highest residual peak was only 0.65 e $Å^{-3}$. A second data collection with a fresh crystal gave an identical result, although the peak represented a slightly smaller residual electron density of 1.3 e $Å^{-3}$.

In all compounds, the non-H-atoms were refined anisotropically. The OH H-atoms of MeOH in **10a** and the amine H-atoms in **10c**, **10d**, and **14a** were placed in the positions indicated by difference-electron-density maps, and their positions were allowed to refine together with an isotropic displacement parameter. All other H-atoms in the structures were fixed in geometrically calculated positions, and each was assigned a fixed isotropic displacement parameter with a value equal to 1.2 U_{eq} of its parent C-atom. Refinement of the structures was carried out on *F* according to full-matrix least-squares procedures, which minimized the function $\Sigma w(|F_O| - |F_C|)^2$. A correction for secondary extinction was applied in the cases of **10a**, **12**, and **14a**. Three, three, and one reflections, whose intensities were considered to be extreme outliers, were omitted from the final refinement of **10c**, **12**, and **14a**, respectively. Neutral atom scattering factors for non-H-atoms were taken from [24a], and the scattering factors for H-atoms were taken from [25]. Anomalous dispersion effects were included in F_c [26]; the values for f' and f'' were those of [24b]. The values of the mass attenuation coefficients are those of [24c]. All calculations were performed with the teXsan crystallographic software package [27].

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[3]) CCDC-229445–229449 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge *via* www.ccdc.cam.ac.uk/conts/retrieving.html (or from the *Cambridge Crystallographic Data Centre*, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033; e-mail: deposit@ccdc.cam.ac.uk)).

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