Reactions of 4-(Diethylamino)selenet-2(2*H*)-imine with Nucleophiles – Synthesis of 2-Methylen-3-oxobutane Selenoamides

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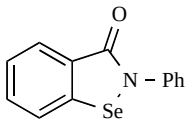
Abstract: 3-Acetyl-*N*-(4-bromophenyl)-4-(diethylamino)selenet-2(2*H*)-imine (**5a**), which is conveniently obtained from the formal [2+2] cycloaddition of 4-bromophenyl isoselenocyanate and 4-(diethylamino)-3-butyn-2-one, reacts with amines, alcohols, water, and thiophenol to give the corresponding 2-methylen-3-oxobutane selenoamides **7** in good yields *via* ring opening to the ketenimine **6** and subsequent addition of the nucleophile.

Keywords: Ketenimines, ring opening, selenet-2(2*H*)-imines, selenium heterocycles, selenoamides, X-ray crystallography.

INTRODUCTION

Selenium is an important element for higher organisms [1]. It is now well known that the selenoenzyme glutathione peroxidase (GPx) acts as an antioxidant, which catalyzes the reduction of harmful peroxides and protects the lipid membranes and other cellular components against oxidative damage [2]. Furthermore, it has been shown that some simple organoselenium compounds are able to mimic the GPx activity *in vitro*. Among them the most promising drug was Ebselen (**1**), a heterocyclic compound that functions as an antioxidant [3], and which is still of high interest because of its biological activities [4, 5] (for recent reviews see [6]). After the discovery of this compound, several other GPx mimics have been reported, *e.g.*, Ebselen analogues [7], benzoselenazolinones [8], cyclic selenamides of type **2** [9], diaryl diselenides [10], and the semisynthetic enzyme selenolsubtilisin [11].



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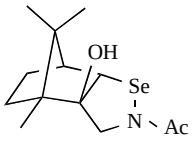

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In recent years, isoselenocyanates have been shown to be useful building blocks for the synthesis of Se-containing heterocycles [12]. For example, the reaction of aryl isoselenocyanates **3** with 4-diethylamino-3-butyn-2-one (**4**) in boiling THF yielded 3-acetyl-*N*-aryl-4-(diethylamino) selenet-2(2*H*)-imines **5** in a formal [2+2] cycloaddition [13] (Scheme **1**). In preliminary experiments it has been shown that these four-membered selenaheterocycles react in boiling THF with morpholine and cyclohexylamine to give the corresponding 2-(diaminomethylene)-*N*,*N*-diethyl-3-oxobutane selenoamides.

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Four-membered selenaheterocycles have been described only scarcely. Whereas several examples of the saturated selenetanes [14] and selenazetidines [15] are known, only a single report on unsaturated 2*H*-selenetes was known [16] when we prepared compounds **5** [13]. The reaction of selenobenzaldehyde complexes **6** with bis(*tert*-butylthio) ethyne (**7**) at low temperature gave the 2*H*-selenete complexes **8**, which were transformed into **9** by treatment with tetraethylammonium bromide (Scheme **1**). Electrocyclic ring opening to the corresponding α,β-unsaturated thioselenocarboxylic esters have been observed for **8** and **9**.

In the present paper, we report on the ring opening reaction of 3-acetyl-*N*-(4-bromophenyl)-3-(diethylamino) selenet-2(2*H*)-imine (**5a**, Ar = 4-BrC_6H_4) [13] with amines, alcohols, water, and thiophenol.

RESULTS AND DISCUSSION

When a solution of 3-acetyl-*N*-(4-bromophenyl)-4-(diethylamino)selenet-2-(2*H*)-imine (**5a**) and excess benzylamine or butylamine in THF was heated to reflux temperature, the 2-(diaminomethylene)-3-oxobutane selenoamide **11a** or **11b**, respectively, was obtained as yellow crystals in fair yield (Scheme **2**, Table **1**). The structures of these products were assigned in analogy to those of the previously reported ones [13]. It is worth mentioning that no 'C=O band' could be detected in the IR spectra (KBr) and the ^{13}C NMR absorptions ($CDCl_3$) for the carbonyl C-atom and the thioamide group appear at 181–179 ppm, indicating that no 'acetyl group' is present. In the ^{1}H NMR spectra, the singlet at 14.4–14.5 ppm indicates a strong intramolecular hydrogen bond. This fact can be explained by the preferred structures of type **11'** or the analogous enolized structure **11''**.

In the case of the reactions of **5a** with alcohols (propan-2-ol, ethanol, butan-1-ol), the respective alcohol was used as the solvent. The products **11c**–**11e** were isolated in 76–54% yield as yellow crystals. Again, there was no indication of an acetyl C=O group in the IR spectra. In the ^{1}H NMR spectra, the signal for the NH, which is involved in the intramolecular hydrogen bond, appeared at 12.6–12.3 ppm

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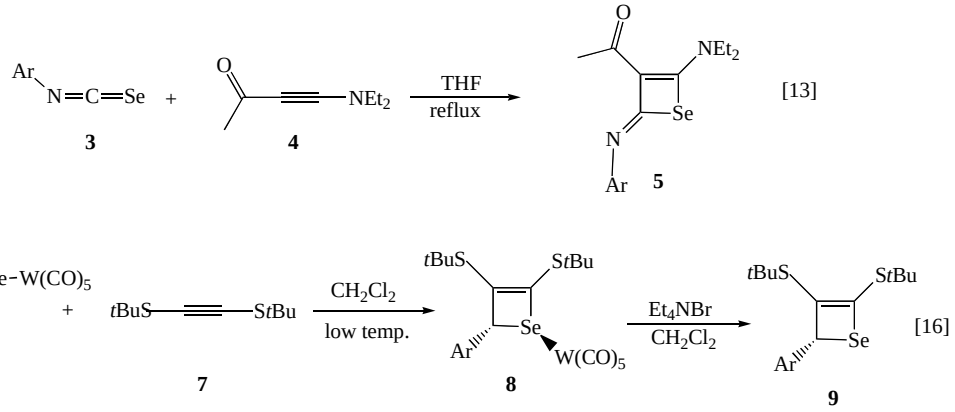
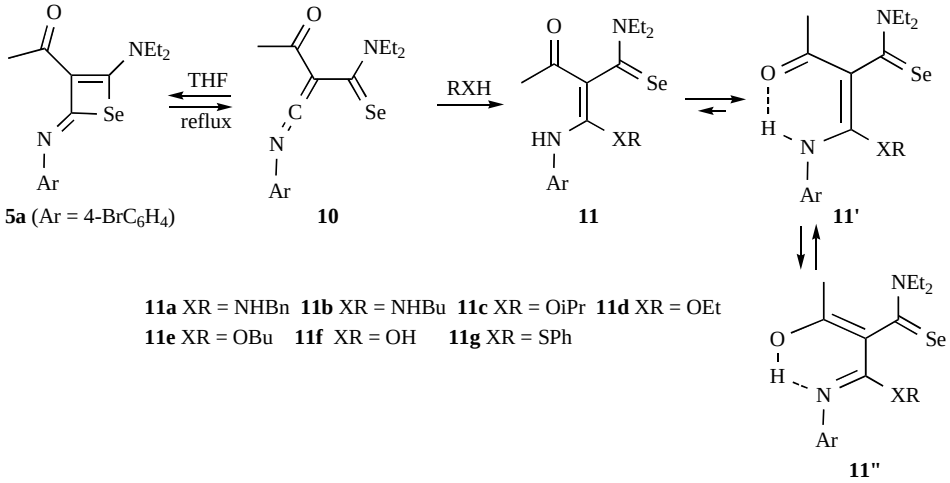
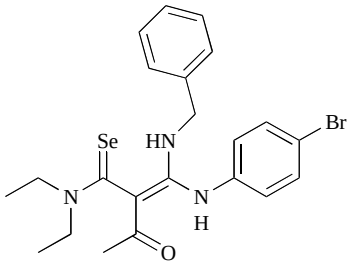
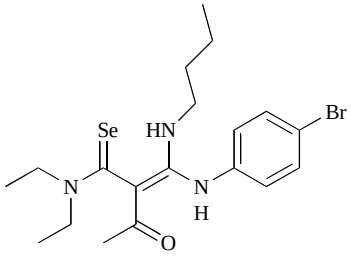


Scheme 1.

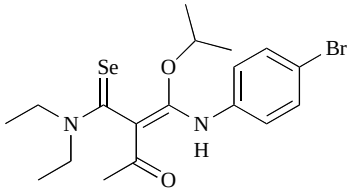
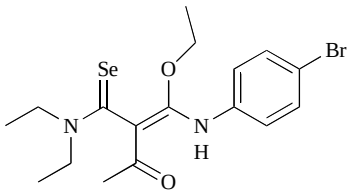
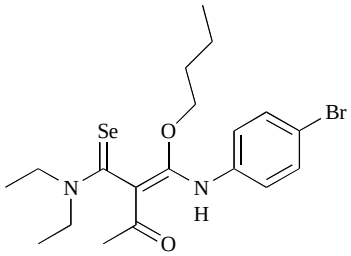
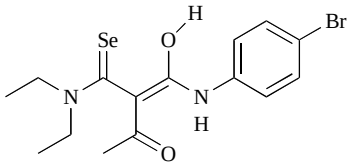
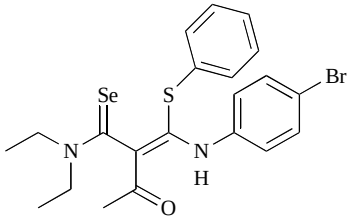


Scheme 2.

Table 1. Preparation of 2-Methylene-3-oxobutane Selenoamides 11 from Selenet-2(2*H*)-imine 5a

	Selenoamides 11	M.p. (°C)	Yield (%)
11a		173.9–175.4	63.2
11b		81.4–82.1	45.7

(Table 1). Contd…..

	Selenoamides 11	M.p. (°C)	Yield (%)
11c		154.6–154.7	73.5
11d		115.4–116.9	75.8
11e		127.5–128.3	54.3
11f		133.4–134.8	71.0
11g		129.1–130.0	59.0

and in the ^{13}C NMR spectra, the carbonyl C-atom and the thioamide group absorb at 200–199 ppm, *i.e*., at significantly lower field than in the amine adducts **11a** and **11b**. For this reason, the structure of **11c** was established by X-ray crystallography. Suitable crystals were obtained from acetonitrile by slow evaporation of the solvent at room temperature. The molecular structure is shown in Fig. (**1**).

In the crystal structure of **11c**, the C(1)–C(2) bond (1.382(3) Å) is somewhat longer than a formal C=C bond (1.34 Å), while the C(1)–N(1) and C(1)–O(1) bonds are quite short (1.349(3) and 1.344(2) Å, respectively) compared with formal C–N and C–O bonds (1.47 and 1.43 Å, respectively). Furthermore, the C(2)–C(13) bond is shorter (1.446(3) Å) than a formal C–C bond (1.54 Å), whereas C(13)–O(13) is slightly longer (1.246(2) Å) than a normal C=O bond (1.22 Å). This indicates significant π-electron delocalisation in this region of the molecule. Nonetheless, the region around C(1)–C(2) bond is quite planar. The C(3)–N(3) bond is also quite short, indicating delocalisation of the C(3)=Se electron density in the thioamide moiety. The NH group forms an intramolecular hydrogen bond with the ketone O-atom (N(1)….O(13) 2.607(2) Å, and N(1)–H….O(13) 141(2)°), thereby creating a six-membered loop with a graph set motif [18] of S(6). These data show that, at least in the crystalline state, the structure for the alcohol adducts **11c**–**11e** is described best with formula **11'** (Scheme **2**).

The reaction of **5a** with water was carried out in THF and the mixture was heated to reflux for 58 h. After evaporation of the solvent and treatment with methanol, **11f** was obtained in 71% yield as a yellow solid. Similarly, the reaction of **5a** with 5 equivalents of thiophenol in boiling THF yielded, after preparative layer chromatography, the yellow crystalline **11g** in 59% yield. The spectroscopic data of these

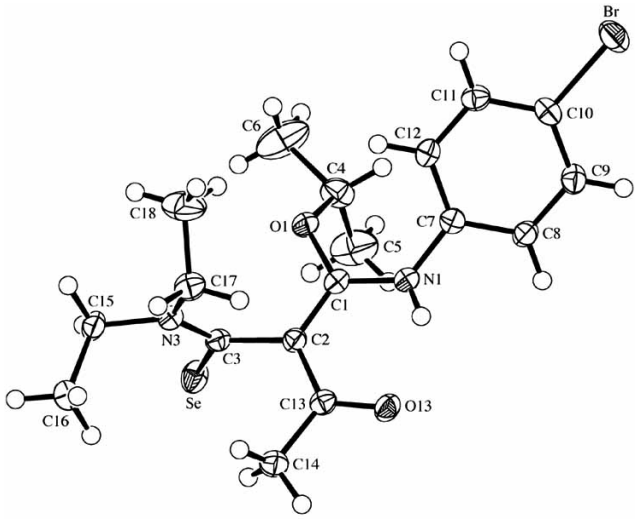


Fig. (1). ORTEP plot [17] of the molecular structure of **11c** (50% probability ellipsoids; arbitrary numbering of atoms).

two products are in good agreement with those of **11a**–**11e** and, therefore, we ascribe the structures **11f'** and **11g'** to the obtained products. It is interesting to note that **11f** possesses the OH group, *i.e.* the enol structure, and does not exist in the tautomeric amide form. This is indicated by a second OH signal in the ^{1}H NMR spectrum at 8.42 ppm.

A reaction mechanism for the formation of the products is proposed in Scheme **2**. Electrocyclic ring opening of the selenete **5a** leads to the ketenimine **10**. Then, nucleophilic addition of amines, alcohols, water or thiophenol onto this reactive intermediates gives the observed adducts **11**.

Our attempts to obtain the products with *tert*-butanol and *tert*-butylamine failed. Probably, the reason is the steric hindrance of the addition of the sterically crowded nucleophiles. The selenete **5a** starts to decompose at temperatures above 90°C and is sensitive to basic media. For example, the attempt to perform the reaction between **5a** and sodium thiophenolate led to complete decomposition of the starting selenete.

In summary, we have shown that the selenete **5a** at elevated temperature undergoes an electrocyclic ring opening generating keteneimine **10** as a reactive intermediate, which can be trapped with N, O, and S-nucleophiles to give *N,N*-diethyl-2-methylene-3-oxobutane selenoamides of type **11**.

EXPERIMENTAL

General

See ref. [19]. TLC: silica gel 60 F_{254} plates (0.25 mm; Merck). Column chromatography (CC): silica gel 60 (0.040-0.063 mm; Merck). Melting Points: Büchi B-540 apparatus, in capillaries; uncorrected. IR spectra in KBr (cm^{-1}). ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.5 MHz) spectra: Bruker ARX-300 instrument in $CDCl_3$; chemical shifts in ppm; multiplicity of C-atoms from DEPT spectra. CI-MS: Finnigan SSQ-700 or MAT-90 instrument; NH_3 as carrier gas; ESI-MS: Finnigan TSQ-700 instrument.

Starting Materials

4-(Bromophenyl)isoselenocyanate was prepared according to the protocol described in ref. [20]. 4-(Diethylamino)-3-butyn-2-one was prepared according to the protocol in ref. [21]. 3-Acetyl-*N*-(4-bromophenyl)-4-(diethylamino)selenet-2(2*H*)-imine was prepared according to the procedure described in ref. [13].

General Procedure for the Reaction of Selenet-2(2*H*)-imine 5a with Amines

To a stirred solution of **5a** in THF, 5 equiv. of benzyl amine or butyl amine, respectively, were added. The mixture was stirred for 2 h under reflux. Then, the solvent was evaporated to dryness under reduced pressure, and the residue was treated with Et_2O (benzyl amine) or CH_2Cl_2/hexane (butylamine). In the case of benzylamine, yellow crystals formed. With butyl amine, the oily glue was purified by preparative TLC (AcOEt/hexane 1:3), the solvent was evaporated, the remaining oil was dissolved in CH_2Cl_2/hexane, the solvent was evaporated under reduced pressure and a yellow solid formed.

2-{[(4-Bromophenyl)amino](benzylamino)methylene}-N,N-diethyl-3-oxobutane Selenoamide (11a)

From 0.3 g (0.75 mmol) of **5a** and 0.40 g (5 equiv.) of benzylamine in THF (25 mL). Yield: 0.24 g (63.2%). M.p. 173.9–175.4°C (Et_2O). IR: 3425*w* (br), 3245*m*, 3173*m*, 3085*m*, 2983*m*, 1606*s*, 1497*s*, 1452*s*, 1400*s*, 1373*s*, 1350*s*, 1267*s*, 1212*m*, 1184*s*, 1169*m*, 1139*s*, 1094*m*, 1067*m*, 1026*m*, 1003*m*. ^{1}H NMR ($CDCl_3$): 14.59 (*s*, NH); 7.76, 7.42 (*AA'BB'*, J_{AB} = 8.8, 4 arom. H); 7.39–7.28 (*m*, 5 arom. H); 6.25 (*t*-like, NH); 4.81 (*dd*, *J* = 14.2, 4.5, 1 H of $PhCH_2$); 4.79 (*dd*, *J* = 14.2, 5.4, 1 H of $PhCH_2$); 3.92–3.42 (*m*, 2 CH_2); 1.73 (*s*, MeCO); 1.38, 1.32 (2*t*, *J* = 7.3, 2 Me). ^{13}C NMR ($CDCl_3$): 181.1 (*s*, CO); 180.4 (*s*, CSe); 167.3, 140.3, 135.7, 118.1, 105.2 (5*s*, 3 arom. C, C(2), C(1')); 131.1, 129.0, 128.5, 125.8 (4*d*, 9 arom. C); 49.7, 47.7 (2*t*, 2 CH_2); 42.2 (*t*, Ph*C*H_2); 26.3 (*q*, *Me*CO); 13.4, 10.1 (2*q*, 2 Me). ESI-MS: 510 (84), 509 (26), 508 (100, $[M+1]^+$), 507 (18), 506 (51), 505 (17). Anal. Calcd for $C_{22}H_{26}BrN_3OSe$ (507.33): C, 52.08; H, 5.17; N, 8.28. Found: C, 51.95; H, 5.19; N, 8.24.

2-{[(4-Bromophenyl)amino](1-butylamino)methylene}-N,N-diethyl-3-oxobutane Selenoamide (11b)

From 0.3 g (0.75 mmol) of **5a**, 0.27 g (5 equiv.) of butylamine in THF (25 mL). Yield: 0.16 g (45.7%), after preparative TLC. M.p. 81.4–82.1°C (CH_2Cl_2/hexane). IR: 3420*w* (br), 3250*m*, 3182*m*, 3100*m*, 2958*s*, 2930*s*, 2870*m*, 1602*s*, 1504*s*, 1373*s*, 1286*s*, 1186*s*, 1152*m*, 1097*m*, 1010*m*. ^{1}H NMR ($CDCl_3$): 14.51 (*s*, NH); 7.68, 7.34 (*AA'*,*BB'*, J_{AB} = 8.8, 4 arom. H); 5.77 (*t*-like, BuN*H*); 3.90–3.74, 3.65–3.33 (2*m* (1:7), 4 CH_2); 1.78 (*s*, *Me*CO); 1.74–1.59 (*m*, CH_2); 1.35, 1.23, 0.88 (3*t*, *J* = 7.3, 3 Me). ^{13}C NMR ($CDCl_3$): 180.4 (*s*,CO); 179.1 (*s*, CSe); 166.5, 139.5, 117.5, 104.5 (4*s*, 2 arom. C, C(2), C(1')); 130.1, 124.8 (2*d*, 4 arom. C); 46.7, 44.5, 41.1, 30.5, 19.1 (5*t*, 5 CH_2); 25.4, 12.8, 12.5, 9.2 (4*q*, 4 Me). CI-MS: 478 (13), 477 (17), 476 (78), 475 (22), 474 (100, $[M+1]^+$), 473 (21), 472 (45), 471 (13), 470 (14), 396 (48), 394 (42), 213 (46). Anal. Calcd for $C_{19}H_{28}BrN_3OSe$

(473.31): C, 48.21; H, 5.96; N, 8.88. Found: C, 48.46; H, 5.59; N, 8.66.

Reactions of Selenet-2(2*H*)-imine 5a with Alcohols

In all of the cases, the respective alcohol was used as a solvent.

2-{[(4-Bromophenyl)amino](isopropoxy)methylene}-N,N-diethyl-3-oxobutane Selenoamide (11c)

A solution of **5a** (0.3 g, 0.75 mmol) in 2-propanol (25 mL) was heated to reflux for 12 h. The solution was concentrated and after cooling to room temperature, crystals formed,which were filtered off. Yield: 0.25 g (73.5%). After preparative TLC (silicagel, hexan/AcOEt 1:1): Yield: 61.8%. Yellow crystals. M.p. 154.6–154.7°C (MeOH). IR: 3425*w* (br), 3085*w*, 3063*w*, 3005*w*, 2974*m*, 2935*m*, 2871*w*, 1614*s*, 1584*s*, 1562*s*, 1488*s*, 1465*m*, 1455*m*, 1431*s*, 1393*m*, 1374*m*, 1356*m*, 1340*m*, 1297*m*, 1284*m*, 1267*s*, 1217*s*, 1178*m*, 1169*m*, 1147*m*, 1122*s*, 1092*s*, 1071*s*, 1054*m*, 1004*m*. ^{1}H NMR ($CDCl_3$): 12.54 (*s*, NH); 7.43, 7.05 (*AA'BB'*, J_{AB} = 8.7, 4 arom. H); 4.57–4.43 (*m*, CH_2); 4.20–4.01 (*m*, CH); 3.74–3.66 (*m*, CH_2); 2.27 (*s*, MeCO); 1.43 (*t*, *J* = 7.1, Me); 1.33–1.26 (*m*, 2 Me); 1.10 (*d*, *J* = 5.9, Me). ^{13}C NMR ($CDCl_3$): 199.8 (*s*, CO); 193.2 (*s*, CSe); 157.8, 137.5, 117.7, 96.2 (4*s*, 2 arom. C, C(2), C(1')); 132.4, 123.6 (2*d*, 4 arom. CH); 76.9 (*d*, Me_2CH); 49.7, 48.2 (2*t*, 2 CH_2); 28.4 (*q*, *Me*CO); 22.9, 22.1, 12.8, 10.7 (4*q*, 4 Me). ESI-MS: 486 (23), 485 (94), 484 (27), 483 (100, $[M+Na]^+$), 482 (24), 481 (52), 480 (18), 479 (20). Anal. Calcd for $C_{18}H_{25}BrN_2O_2Se$ (460.27): C, 46.97; H, 5.47; N, 6.09. Found: C, 47.20; H, 5.55; N, 6.05.

Suitable crystals of **8a** for the X-ray crystal structure determination were obtained from MeCN by slow evaporation of the solvent at room temperature.

2-{[(4-Bromophenyl)amino](ethoxy)methylene}-N,N-diethyl-3-oxobutane Selenoamide (11d)

A solution of **5a** (0.3 g, 0.75 mmol) in abs. EtOH (25 mL) was heated to reflux for 8 h. Then, the solvent was removed, the oily residue was treated with MeOH, and a yellow solid formed, which was purified by preparative TLC (AcOEt/hexane 1:3). The solvent was removed, the obtained oily product was treated with MeOH, and the solid material formed was recrystallized from Et_2O/hexane, by cooling in an ice bath. Yield: 0.25 g (75.8%). After preparative TLC, yield 60.1%. Yellow crystals. M.p. 115.4–116.9 (Et_2O/hexane). IR: 3423*w* (br), 3084*w*, 3059*w*, 3026*w*, 2980*m*, 2934*m*, 2870*w*, 1614*s*, 1582*s*, 1550*s*, 1487*s*, 1465*m*, 1454*m*, 1425*s*, 1379*s*, 1359*s*, 1344*s*, 1287*m*, 1271*m*, 1217*s*, 1192*m*, 1169*m*, 1119*m*, 1094*m*, 1069*m*, 1052*s*, 1005*s*. ^{1}H NMR ($CDCl_3$): 12.37 (*s*, NH); 7.44, 7.08 (*AA'BB'*, *J* = 8.7, 4 arom. H); 4.40–4.10, 3.95–3.66 (2*m*, 3 CH_2); 2.23 (*s*, MeCO); 1.43, 1.29 (2*t*, *J* = 7.0, 2 Me); 1.19 (*t*, *J* = 7.0, Me). ^{13}C NMR ($CDCl_3$): 199.0 (*s*, CO); 193.1 (*s*, CSe); 158.8, 136.8, 117.6, 93.2 (4*s*, 2 arom. C, C(2), C(1')); 132.3, 123.1 (2*d*, 4 arom. CH); 68.8 (*t*, CH_2O); 49.8, 48.2 (2*t*, 2 CH_2); 27.7 (*q*, *Me*CO); 14.8, 12.6, 10.5 (3*q*, 3 Me). CI-MS: 451 (13), 450 (15), 449 (78), 448 (21), 447 (100, $[M+1]^+$), 446 (21), 445 (46), 444 (15), 443 (14), 418 (12), 369 (16), 367 (16), 294 (20), 292 (10). Anal. Calcd for $C_{17}H_{23}BrN_2O_2Se$ (446.24): C, 45.76; H, 5.20; N, 6.28. Found: C, 45.60, H, 5.15, N, 6.27.

2-{[(4-Bromophenyl)amino](1-butoxy)methylene}-N,N-diethyl-3-oxobutane Selenoamide (11e)

A solution of **5a** (0.3 g, 0.75 mmol) in 1-butanol (20 mL) was stirred at 80°C for 5 h. The solvent was evaporated, the oily residue treated with MeOH, the solid formed was purified by preparative TLC (AcOEt/hexane 1:3), and the oily product, after evaporation of the solvent, was treated with MeOH to give yellow crystals. Yield: 0.19 g (54.3%), after preparative TLC. Yellow crystals. M.p. 127.5–128.3 (MeOH). IR: 3442*w* (br), 2955*m*, 2920*m*, 2870*m*, 1617*s*, 1584*s*, 1556*s*, 1484*s*, 1431*s*, 1377*s*, 1266*s*, 1200*s*, 1118*m*, 1097*m*, 1059*s*, 1003*m*. ^{1}H NMR ($CDCl_3$): 12.36 (*s*, NH); 7.44, 7.07 (*AA'B,B'*, J_{AB} = 8.8, 4 arom. H); 4.42–4.08, 3.88–3.58 (2*m*, 3 CH_2); 2.21 (*s*, MeCO); 1.60–1.51 (*m*, CH_2); 1.43 (*t*, *J* = 6.9, Me); 1.30 (*m*, CH_2, Me); 0.84 (*t*, *J* = 7.3, Me). ^{13}C NMR ($CDCl_3$): 199.1 (*s*, CO); 192.1 (*s*, CSe); 159.0, 136.7, 117.6, 110.1 (4*s*, 2 arom. C, C(2), C(1')); 132.2, 123.2 (2*d*, 4 arom. C); 72.5, 49.8, 48.2, 31.3, 18.6 (5*t*, 5 CH_2); 27.7, 13.6, 12.6, 10.6 (4*q*, 4 Me). CI-MS: 479 (14), 478 (17), 477 (77), 476 (23), 475 (100, $[M+1]^+$), 474 (21), 473 (46), 472 (14), 471 (13), 421 (10), 419 (12), 403 (18), 401 (19), 397 (16), 395 (16). Anal. Calcd for $C_{19}H_{22}BrN_2O_2Se$ (474.29): C, 48.11; H, 5.74; N, 5.91. Found: C, 48.81; H, 5.56; N, 5.83.

Reaction of Selenet-2(2*H*)-imine 5a with Water

To a solution of **5a** (0.3 g, 0.75 mmol) in THF (25 mL), H_2O (0.5 mL) was added, and the mixture heated to reflux for 58 h. The solvent was removed, the remaining oily glue was treated with MeOH, and a yellow solid formed.

2-{[(4-Bromophenyl)amino](hydroxy)methylene}-N,N-diethyl-3-oxobutane Selenoamide (11f)

Yield: 0.22 g (71%). Yellow crystals. M.p. 133.4–134.8°C (MeOH). IR: 3442*w* (br), 3304*m*, 3109*w*, 3047*w*, 3008*m*, 2924*s*, 2853*m*, 1630*s*, 1600*s*, 1585*s*, 1529*s*, 1489*s*, 1439*s*, 1425*s*, 1396*s*, 1378*s*, 1358*m*, 1334*s*, 1302*s*, 1241*s*, 1217*s*, 1126*s*, 1094*m*, 1074*s*, 1008*m*. ^{1}H NMR ($CDCl_3$): 13.96 (*s*, NH); 8.42 (*s*, OH); 7.43, 7.35 (*AA'BB'*, J_{AB} = 8.9, 4 arom. H); 4.68–4.52, 4.00–3.75, 3.60–3.45 (3*m* (1:2:1), 2 CH_2); 1.93 (*s*, MeCO); 1.42 (*t*, *J* = 7.1, Me); 1.22 (*t*, J = 7.2, Me). ^{13}C NMR ($CDCl_3$): 197.5 (*s*, CO); 167.9 (*s*, CSe); 167.1, 136.1, 117.5, 110.8 (4*s*, 2 arom. C), C(2), C(1')); 132.0, 122.2 (2*d*, 4 arom. C); 50.7, 48.6 (2*t*, 2 CH_2); 19.7 (*q*, *Me*CO); 12.9, 10.7 (2*q*, 2 Me). CI-MS: 423 (13), 422 (14), 421 (80), 420 (19), 419 (100, $[M+l]^+$), 418 (21), 417 (47), 416 (16), 415 (15), 405 (10), 403 (20), 401 (19), 341 (43), 339 (42), 248 (14), 222 (16). Anal. Calcd for $C_{15}H_{19}BrN_2O_2Se$ (418.19): C, 43.08; H, 4.58; N, 6.70. Found: C, 43.92, H, 4.79; N, 6.50.

Reaction of Selenet-2(2*H*)-imine 5a with Thiophenol

A solution of **5a** (0.3 g, 0.75 mmol) and thiophenol (0.4 g, 3.6 mmol, ca. 5 equiv.) in THF (25 mL) was heated to reflux for 11 h. Then, the solvent was removed under reduced pressure, the remaining oily residue was treated with MeOH, and a yellow solid formed, which was purified by preparative TLC (AcOEt/hexane 1:3). After evaporation of the solvent, the oily product was again treated with MeOH to obtain yellow crystals.

2-{[(4-Bromophenyl)amino](phenylsulfanyl)methylene}-N,N-diethyl-3-oxobutane Selenoamide (11g)

Yield: 0.22 g (59%, after preparative TLC). M.p. 129.1–130.0°C (MeOH). IR: 3422*w* (br), 3054*w*, 2976*m*, 2937*m*, 2852*m*, 1595*s*, 1580*s*, 1556*s*, 1515*s*, 1486*s*, 1472*m*, 1440*m*, 1402*m*, 1366*s*, 1346*s*, 1326*m*, 1280*s*, 1269*s*, 1213*m*, 1184*m*, 1174*m*, 1150*m*, 1112*m*, 1102*m*, 1079*m*, 1065*m*, 1020*m*, 1005 *m*. ^{1}H NMR ($CDCl_3$): 13.78 (*s*, NH); 7.84 (*AA'* of *AA'BB'*, J_{AB} = 8.4, 2 arom. H); 7.50–7.35 (*m*, 7 arom. H); 4.35–4.20, 4.20–3.90, 3.85–3.70 (3*m* (1:2:1), 2 CH_2); 1.85 (*s*, MeCO); 1.66, 1.42 (2*t*, *J* = 7.2, 7.3, 2 Me). ^{13}C NMR ($CDCl_3$): 193.6 (*s*, CO); 181.5 (*s*, CSe); 178.8, 139.9, 125.8, 117.9, 110.0 (5*s*, 3 arom. C, C(2), C(1')); 135.5, 131.6, 131.2, 129.2, 126.3 (5*d*, 9 arom. C); 52.3, 48.1 (2*t*, 2 CH_2); 27.1 (*q*, *Me*CO); 12.3, 9.3 (2*q*, 2 Me). CI-MS: 511 (<1, $[M+1]^+$), 483 (1.5), 481 (2), 479 (1.5), 405 (11), 404 (12), 403 (77), 402 (16), 401 (100, $[M\text{-PhS}]^+$), 400 (17), 399 (42), 398 (11), 397 (12), 323 (12). Anal. Calcd for $C_{21}H_{23}BrN_2OSSe$ (510.35): C, 49.42; H, 4.54; N, 5.49. Found: C, 49.23; H, 4.42; N, 5.37.

Crystal-Structure Determination of 11c [22]

All measurements were made on a *Nonius KappaCCD* area-detector diffractometer [23] using graphite-monochromated MoK_α radiation (λ 0.71073 Å) and an *Oxford Cryosystems Cryostream 700* cooler. Data reduction was performed with *HKL Denzo* and *Scalepack* [24]. The intensities were corrected for Lorentz and polarization effects, and an absorption correction based on the multi-scan method [25] was applied. Equivalent reflections were merged. Data collection and refinement parameters are given in [26]. A view of the molecule is shown in Fig. (**1**). The structure was solved by direct methods using *SIR92* [27], which revealed the positions of all non-hydrogen atoms. The non-hydrogen atoms were refined anisotropically. The amine H-atom was placed in the position indicated by a difference electron density map and its position was allowed to refine together with an isotropic displacement parameter. All remaining H-atoms were placed in geometrically calculated positions and refined using a riding model where each H-atom was assigned a fixed isotropic displacement parameter with a value equal to 1.2U_{eq} of its parent C-atom (1.5U_{eq} for the methyl groups). Refinement of the structure was carried out on F^2 using full-matrix least-squares procedures, which minimized the function $\Sigma w(F_o^2 - F_c^2)^2$. A correction for secondary extinction was not applied. Neutral atom scattering factors for non-hydrogen atoms were taken from [28a], and the scattering factors for H-atoms were taken from [29]. Anomalous dispersion effects were included in F_c [30]; the values for *f'* and *f"* were those of [28b]. The values of the mass attenuation coefficients are those of [28c]. All calculations were performed using the *SHELXL97* [31] program.

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REFERENCES

[1] Rayman, M.P. The importance of selenium to human health. *Lancet*, **2000**, *356*, 233.

[2] (a) Flohé, L. The glutathione peroxidase reaction: molecular basis of the antioxidant function of selenium in mammals. *Curr. Top. Cell Regul.*, **1985**, *27*, 473; (b) Burk, R.F. *Selenium in Biology and Human Health*, Springer-Verlag: New York, **1994**.

[3] (a) Müller, A.; Cadenas, E.; Graf, P.; Sies, H. A novel biologically active seleno-organic compound I: glutathione peroxidase-like activity *in vitro* and antioxidant capacity of PZ 51 (Ebselen). *Biochem. Pharmacol.*, **1984**, *33*, 3235; (b) Wendel, A.; Fausel, M.; Safayhi, H.; Tiegs, G.; Otter, R. A novel biologically active seleno-organic compound II. Activity of PZ 51 in relation to glutathione peroxidase. *Biochem. Pharmacol.*, **1984**, *33*, 3241; (c) Parnham, M.J.; Kindt, S. A novel biologically active seleno-organic compound III. Effects of PZ 51 (Ebselen) on glutathione peroxidase and secretory activities of mouse macrophages. *Biochem. Pharmacol.*, **1984**, *33*, 3247.

[4] (a) Parnham. M.; Sies, H. Ebselen: prospective therapy for cerebral ischaemia. *Expert. Opin. Investig. Drugs*, **2000**, *9*, 607; (b) Nakamura, Y.; Feng, Q.; Kumagai, T.; Torikai, K.; Ohigashi, H.; Osawa, T.; Noguchi, N., Niki, E., Uchida, K. Ebselen, a glutathione peroxidase mimetic seleno-organic compound, as a multifunctional antioxidant: implication for inflammation-associated carcinogenesis. *J. Biol. Chem.*, **2002**, *277*, 2687; (c) Hardej, D.; Billack, B. Ebselen protects brain, skin, lung and blood cells from mechlorethamine toxicity. *Toxicol. Ind. Health*, **2007**, *23*, 209; (d) Yamagata, K.; Ichinose, S.; Miyashita, A.; Tagami, M. Protective effects of ebselen, a seleno-organic antioxidant, on neurodegeneration induced by hypoxia and reperfusion in stroke-prone spontaneously hypertensive rat. *Neuroscience*, **2008**, *153*, 428; (e) Miorelli, S.T.; Rosa, R.M.; Moura, D.J.; Rocha, J.C.; Lobo, L.A.C.; Henriques, J.A.P.; Saffi, J. Antioxidant and anti-mutagenic effects of ebselen in yeast and in cultured mammalian V79 cells. *Mutagenesis*, **2008**, *23*, 93; (f) Nishina, A.; Sekiguchi, A.; He, Y.; Koketsu, M.; Furukawa, S. Ebselen, a redox regulator containing a selenium atom, induces neurofilament M expression in cultured rat pheochromocytoma PC12 cells *via* activation of mitogen-activated protein kinase. *J. Neurosci. Res.*, **2008**, *86*, 720.

[5] Pearson, J.K.; Boyd, R.J. Effect of substituents on the GPx-like activity of ebselen: steric *versus* electronic. *J. Phys. Chem. A*, **2008**, *112*, 1013.

[6] (a) Mugesh, G.; du Mont, W.-W.; Sies, H. Chemistry of biologically important synthetic organoselenium compounds. *Chem. Rev.*, **2001**, *101*, 2125; (b) Soriano-Garcia, M. Organoselenium compounds as potential therapeutic and chemopreventive agents: a review. *Curr. Med. Chem.*, **2004**, *11*, 1657; (c) Mlochowski, J.; Kloc, K.; Lisiak, R.; Potaczek, P.; Wojtowicz, H. Developments in the chemistry of selenaheterocyclic compounds of practical importance in synthesis and medicinal biology. *Arkivoc*, **2007**, *vi*, 14.

[7] (a) Jacquemin, P.V.; Christiaens, L.E.; Renson, M.J.; Evers, M.J.; Dereu, N. Synthesis of 2*H*-3,4-dihydro-1,2-benzoselenazin-3-one and derivatives: a new heterocyclic ring system. *Tetrahedron Lett.*, **1992**, *33*, 3863; (b) Chaudière, J.; Jadan, J.-C.; Erdelmeier, I.; Tailham-Lomont, C.; Moutet, M. In *Oxidative Processes and Antioxidants*; Paoletti, R.; Ed.; Raven Press: New York, **1994**; p. 165; (c) Chaudière, J.; Moutet, M.; d'Alessio, P. Antioxidant and anti-inflammatory protection of vascular endothelial cells by new synthetic mimics of glutathione peroxidase. *C. R. Soc. Biol.*, **1995**, *189*, 861; (d) Sies, H. Ebselen, a selenoorganic compound as glutathione peroxidase mimic. *Free Radic. Biol. Med.*, **1993**, *14*, 313.

[8] Galet, V.; Bernier, J.-L.; Hénichart, J.-P.; Lesieur, D.; Abadie, C.; Rochette, L.; Lindenbaum, A.; Chalas, J.; Renaud de la Faverie, J.-F.; Pfeiffer, B.; Renard, P. Benzoselenazolinone derivatives designed to be glutathione peroxidase mimetics feature inhibition of cyclooxygenase/5-lipoxygenase pathways and anti-inflammatory activity. *J. Med. Chem.*, **1994**, *37*, 2903.

[9] (a) Back, T.G.; Dyck, B.P. A novel camphor-derived selenamide that acts as a glutathione peroxidase mimetic. *J. Am. Chem. Soc.*, **1997**, *119*, 2079; (b) Reich, H.J.; Jasperse, C.P. Organoselenium chemistry: preparation and reactions of 2,4,6-tri(*tert*)-butylbenzeneselenenic acid. *J. Am. Chem. Soc.*, **1987**, *109*, 5549.

[10] (a) Wilson, S.R.; Zucker, P.A.; Huang, R.-R.C.; Spector, A. Development of synthetic compounds with glutathione peroxidase

activity. *J. Am. Chem. Soc*., **1989**, *111*, 5936; (b) Iwaoka, M.; Tomoda, M.S. *J. Am. Chem. Soc*., **1994**, *116*, 2557; (c) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc*., **1996**, *118*, 8017; (d) Spector, A.; Wilson, S.R.; Zucker, P.A.; Huang, R.-R.C.; Raghavan, P.R. The synthesis of glutathione peroxidase analogs. *Lens Eye Toxic. Res.*, **1989**, *6*, 773.

[11] (a) Wu, Z.-P.; Hilvert, D. Conversion of a protease into an acyltransferase: selenolsubtilisin. *J. Am. Chem. Soc*., **1989**, *111*, 4513; (b) Wu, Z.-P.; Hilvert, D. Selenosubtilisin as a glutathione peroxidase mimic. *J . Am. Chem. Soc*., **1990**, *112*, 5641.

[12] (a) Maeda, H.; Kambe, N.; Sonoda, N.; Fujiwara, S.-I.; Shin-ike, T. Synthesis of 1,3-selenazoles and 2-imidazoline-5-selones from isoselenocyanates and isocyanides. *Tetrahedron*, **1997**, *53*, 13667; (b) Petrov, M.L.; Zmitrovich, N.I. Organic isoselenocyanates. *Russ. J. Gen. Chem*., **1999**, *69*, 245; (c) Garud, D.R.; Koketsu, M.; Ishihara, H. Isoselenocyanates: a powerful tool for the synthesis of selenium-containing heterocycles. *Molecules*, **2007**, *17*, 504; (d) Heimgartner, H.; Zhou, Y.; Atanassov, P.K.; Sommen, G.L. Isoselenocyanates as building blocks for selenium heterocycles. *Phosphorus Sulfur Silicon*, **2008**, *183*, 840.

[13] Atanassov, P.K.; Linden, A.; Heimgartner, H. Synthesis of 3-acyl-*N*-aryl-4-diethylaminoselenet-2(2*H*)-imines from 4-diethylamino-3-butyn-2-one and aryl isoselenocyanates. *Heterocycles*, **2004**, *62*, 521.

[14] (a) Detty, H.R. Four-membered rings with one selenium or tellurium atom. *Comp. Heterocycl. Chem. II*, **1996**, *1B*, 823; (b) Block, E.; Linderman, R.J. Four-membered rings with one oxygen, sulfur, or selenium atom. *Rodd's Chem. Carbon Compds.* 2nd ed., **1997**, *4*, 113; (c) Korotkikh, N.I. Recyclization in the synthesis of heterocyclic compounds with small rings. *Ross. Khim. Zhurnal*, **1999**, *43*, 138; (d) Korotkikh, N.I.; Aslanov, A.F.; Raenko, G.F.; Shvaika, O.P. Halocyclization and recyclization reactions: synthesis of thiirane, thietane, and selenetane derivatives of azolones. *Russ. J. Org. Chem.*, **1999**, *35*, 730; (e) Block, E. Product class 25: selenetanes and derivatives. *Sci. Synth.*, **2007**, *39*, 1033.

[15] (a) Sommen, G.L.; Linden, A.; Heimgartner, H. Selenium-containing heterocycles from isoselenocyanates: cycloaddition of carbodiimides to selenazetidines. *Helv. Chim. Acta*, **2005**, *88*, 766; (b) Koketsu, M.; Yamamura, Y.; Ando, H.; Ishihara, H. Synthesis of 1,3-selenazetidines and 4*H*-1,3,5-oxadiazines using acyl isoselenocyanates. *Heterocycles*, **2006**, *68*, 1267; (c) Koketsu, M.; Otsuka, T.; Ishihara, H. Synthesis of 1,3-selenazetidine derivatives from imines and thiocarbamoyl isoselenocyanate. *Heterocycles*, **2006**, *68*, 2107.

[16] Fischer, H.; Treier, K.; Troll, C.; Stumpf, R. Synthesis of the first 2*H*-selenete complexes, decomplexation and dimerization to dihydro-1,2-diselenine. *J. Chem. Soc., Chem. Commun.*, **1995**, 2461.

[17] Johnson, C.K. *ORTEP II*, Report ORNL-5138, Oak Ridge National Laboratory, Oak Ridge, Tennessee, **1976**.

[18] Bernstein, J.; Davis, R.E.; Shimoni, L.; Chang, N.-L. Patterns in hydrogen bonding: functionality and graph set analysis in crystals. *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1555.

[19] Zhou, Y.; Heimgartner, H. Selenium-containing heterocycles from isoselenocyanates: synthesis of 1,2,3-selenadiazole derivatives. *Helv. Chim. Acta* **2000**, *83*, 539.

[20] (a) Barton, D.H.R., Parekh, S.I., Tajbakhsh, M., Theodorakis, E.A., Tse, C.-L. A convenient and high yielding procedure for the preparation of isoselenocyanates: synthesis and reactivity of *O*-alkylselenocarbamates. *Tetrahedron*, **1994**, *50*, 639; (b) Bakhsh, M.T.; Behshtiha, Y.S.; Heravi, M.M. A facile method for the preparation of isoselenocyanates. *J. Chem. Soc. Pak.*, **1996**, *18*, 159.

[21] Lienhard, U., Fahrni, H.-P., Neuenschwander, M. Substituted aminoacyl derivatives. 12. 'Push-pull' acetylenes as reagents for peptide synthesis. *Helv. Chim. Acta*, **1978**, *61*, 1609.

[22] CCDC-760974 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre CCDC *via* http://www.ccdc.ac.uk/data_request/cif.

[23] Hooft, R. *KappaCCD Collect Software*, Nonius BV, Delft, The Netherlands, **1999**.

[24] Otwinowski, Z., Minor, W. In Methods in Enzymology, Part A, Carter, C.W. Jr.; Sweet, R.M., Eds.; *Macromolecular Crystallography*, Academic Press: New York, **1997**, Vol. *276*, p. 307.

[25] Blessing, R.H. An empirical correction for absorption anisotropy. *Acta Crystallogr., Sect A*, **1995**, *51*, 33.

[26] Crystallographic data for compound **7c**: Empirical formula: $C_{18}H_{25}BrN_2O_2Se$; formula weight: 460.21 g mol^{-1}; crystal color, habit: yellow, prism; crystal dimensions: 0.15 × 0.15 × 0.30 mm; temperature: 160(1) K; crystal system: monoclinic; space group: $P2_1/c$; $Z = 4$; reflections for cell determination: 36745; 2θ range for cell determination: 4 – 60°; unit cell parameters: a = 7.7249(1) Å, b = 23.6372(4) Å, c = 11.5504(2) Å, β = 104.6835(9)°, V = 2040.17(6) Å^3, D_x = 1.498 g cm^{-3}; μ(MoK_α) = 3.816 mm^{-1}; scan type: ϕ and ω; $2\theta_{(max)}$ = 60°; transmission factors (min; max): 0.409; 0.572; total reflections measured: 46394; symmetry independent reflections: 5939; reflections with $I > 2\sigma(I)$: 4389; reflections used in refinement: 5939; parameters refined: 226; final $R(F)$ [$I > 2\sigma(I)$ reflections]:0.0354; $wR(F^2)$ (all data): 0.0783; weights: $w = [\sigma^2(F_o^2) + (0.0308P)^2 + 1.0827P]^{-1}$ where $P = (F_o^2 + 2F_c^2)/3$; goodness of fit: 1.031; final Δ_{max}/σ = 0.004; $\Delta\rho$ (max; min) = 0.49; –0.58 [e Å^{-3}].

[27] Altomare, A.; Cascarano, G.; Giacovazzo, C.; Guagliardi, A.; Burla, M.C.; Polidori, G.; Camalli, M. SIR92 – a program for automatic solution of crystal structures by direct methods. *J. Appl. Crystallogr*., **1994**, *27*, 435.

[28] (a) Maslen, E.N.; Fox, A.G.; O'Keefe, M.A. In International Tables for Crystallography, Wilson, A.J.C., Ed.; Kluwer Academic Publishers: Dordrecht, **1992**, Vol. C, Table 6.1.1.1, p. 477; b) Creagh, D.C.; McAuley, W.J. *ibid*., Table 4.2.6.8, p. 219; c) Creagh, D.C.; Hubbell, J.H. *ibid*., Table 4.2.4.3, p. 200.

[29] Stewart, R.F.; Davidson, E.R.; Simpson, W.T. Coherent X-ray scattering for the hydrogen atom in the hydrogen molecule. *J. Chem. Phys.*, **1965**, *42*, 3175.

[30] Ibers, J.A.; Hamilton, W.C. Dispersion corrections and crystal structure refinements. *Acta Crystallogr.*, **1964**, *17*, 781.

[31] Sheldrick, G. M. *SHELXL97, Program for the Refinement of Crystal Structures*. University of Göttingen: Germany, **1997**.