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# *N*-Propionyl-1,2-benzisoselenazol-3(2*H*)-one

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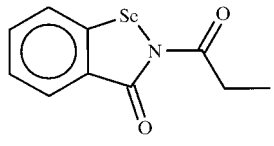
The title compound, $C_{10}H_9NO_2Se$, crystallizes as flat molecules linked by selenium–oxygen interactions [Se···O = 3.189 (4) Å] into a linear chain along the *a* axis of the triclinic cell. The bond dimensions that are derived from *ab initio* geometry optimization calculations are similar to those determined from the diffraction measurements.

## Comment

In glutathione peroxidase (GSH-Px), the enzyme that catalyzes the reduction of hydroperoxides (Parnham & Graf, 1987; Parnham *et al.*, 1986), the selenocysteine residues prevent the generation of free radicals from the hydroperoxides (Magee, 1996). This property of GSH-Px is imitated by the synthetic compound *N*-methyl-1,2-benzisoselenazol-3(2*H*)-one and also by *N*-phenyl-1,2-benzisoselenazol-3(2*H*)-one, which elicits immuno-stimulating action (Inglot *et al.*, 1996). A large number of other derivatives have been synthesized (Welter *et al.*, 1986); the phenyl derivative, ebselen, is the most active, but it is only mildly toxic, its $LD_{50}$ being in the order of g $kg^{-1}$ (Cantineau *et al.*, 1986). The *N*-methyl (Piatek *et al.*, 1995),




(I)

*N*-phenyl (Dupont *et al.*, 1990), 7-nitro-*N*-phenyl (Dupont *et al.*, 1988) and *N*-[2-(ethyl 4-methylvalerate)] (Xiao *et al.*, 1997) derivatives have been structurally documented; these compounds feature molecules that are linked into chains by short intermolecular selenium–oxygen [Se···O = 2.569 (3)–2.812 (5) Å] interactions; however, the reason for such simple compounds to mimic GSH-Px is not apparent from their crystal structures. The title compound, (I), which is a potential immuno-stimulant (Mhizha & Mlochowski, 1997), has an exocyclic amido group that can compete with the endocylic amido group in forming chains; its solid-state structure is compared with the structure that is derived theoretically from geometry optimization calculations.

Compound (I) crystallizes as a flat molecule (r.m.s.d. = 0.0266 Å) (Fig. 1). Adjacent molecules are linked by selenium–oxygen interactions involving the endocyclic carbonyl O atom [Se···O = 3.189 (4) Å] into infinite linear chains. The five-membered isoselenazolyl ring is severely strained at the Se atom [Se—N = 1.876 (3), Se—C = 1.890 (4) Å and N—Se—C = 85.2 (2)°]; the bond dimensions of this atom are similar to those found in *N*-methyl-1,2-benzisoselenazol-3(2*H*)-one (Piatek *et al.*, 1995) and *N*-phenyl-1,2-benzisoselenazol-3(2*H*)-one (Dupont *et al.*, 1990). The angle at selenium in these compounds contrasts with the wider angle found in dipyridylselenium, whose Se atom does not belong to a ring: C—Se—C = 101.9 (2)° in the 2-pyridyl derivative (Dunne *et al.*, 1995) and 100.4 (1)° in the 4-pyridyl derivative (Dunne *et al.*, 1996); large angles are also noted in the biologically active compounds *N*-[(*N*-succimidyl)benzyl]selenamorpholine [C—Se—C = 92.9 (2)°], whose Se atom belongs to a six-membered ring (Wu *et al.*, 1998), and 8-chloro-11-(4-methylpiperazin-1-yl)dibenzo[*b*,*f*]-1,4-selenazepine [C—Se—C = 92.7 (1)°], whose Se atom belongs to a seven-membered ring (Dupont *et al.*, 1999).

In compound (I), in addition to forming a weak oxygen–selenium interaction, the endocyclic carbonyl O atom is 2.42 Å from the H atom attached to the C2 atom of an adjacent molecule. In the *N*-methyl analog, the corresponding distances are Se···O = 2.600 (3) and O···H = 2.31 Å, which give rise to a zigzag chain that propagates along the *c* axis of the monoclinic unit cell. On the other hand, a similar set of interactions, Se···O = 2.569 (3) and O···H = 2.34 Å, results in the formation of a helical chain in the *N*-phenyl derivative. The *N*-propionyl-1,2-benzisoselenazol-3(2*H*)-one molecules are packed such that the entire chain is flat, so that in order to maintain the oxygen–hydrogen linkage, the structure adopts a compromise by lengthening the selenium–oxygen linkage. The weak C—H···O interactions in the three structures are better regarded as electrostatic rather than as van der Waals interactions (Iyere *et al.*, 1998; Ng, 1999).

The *ab initio* calculations yield bond dimensions that are similar to those found in the X-ray structure. As noted from the partial atomic charges (Table 1), the *N*-methyl group in place of the propionyl group causes a decrease of the negative charge on the substitution center (*i.e.* the N atom), and this, in turn, results in a slight increase of electron density at both the C7 and O1 atoms (the C7 atom becomes less positive whereas the O1 atom becomes more negative). Such electron redistribution contributes to a decrease of the bond order and lengthening of the C—O bond in the (endocyclic) carbonyl group. The calculated C—O distance in *N*-methyl-2-benzisoselenazol-3(2*H*)-one (1.220 Å) exceeds that [experimental

C—O = 1.207 (5) Å, calculated C—O = 1.215 Å] in the *N*-propionyl analog. The structural differences among the three *N*-substituted 1,2-benzisoselenazol-3(2*H*)-ones should be taken into consideration when relating the structures of the compounds to their biological activity, as the presence of a second carbonyl group (in the *N*-propionyl derivative) can alter the biological activity.

The structure displays a small N—Se—C angle [experimental 85.2 (2)°, calculated 85.0°] that probably results from the tendency of the ring system to preserve its planarity. The small internal angle at the Se atom and the corresponding ring strain may play some role in the eventual opening of the ring of this and other 1,2-benzisoselenazol-3(2*H*)-ones in chemical reactions (Litvinov & Dyachenko, 1997) or in biological systems.

In contrast to the other structurally verified *N*-substituted benzisoselenazol-3(2*H*)-ones (*i.e.* methyl-, phenyl- and ethyl-4-methylvalerate-), the *N*-propionyl analogue does not exhibit short intermolecular contacts of the Se···O type in the solid state. In the simpler *N*-methyl compound, the relative positive partial charges within the endocyclic carbonyl group (0.314) (calculated as the sum of the relative partial charges of C7 and O1) and on the Se atom (0.851) are smaller than the corresponding values (0.345 and 0.913) of the *N*-propionyl compound. The intermolecular repulsive forces between the endocyclic carbonyl group and the Se atom of adjacent molecules of the *N*-propionyl compound should therefore be larger than the forces in the methyl analogue.

The endocyclic C—N distances [experimental 1.414 (5) Å, calculated 1.387 Å] in *N*-propionyl-1,2-benzoselenazol-3(2*H*)-one are appreciably larger than the mean C—N distance (1.332 Å) obtained from a Cambridge Structural Database (Allen & Kennard, 1993) survey of the C—C(═O)—N*R*—C$sp^3$ fragment in the crystal structures of *cis*-δ-lactams (Chakrabarti & Dunitz, 1982). The long C—N bond is a consequence of the presence of the Se atom in the five-membered ring, which is constrained to be planar. In (3α*R*)-(3α,4α,7α,7aα)-2-acetyl-4,8,8-trimethylperhydro-4,7-methano-1,2-benzisoselenazol-3a-ol, the five-membered heterocyclic isoselenazolyl ring adopts an envelope shape [Se—N = 1.865 (3), Se—C = 1.943 (3) Å and N—Se—C = 87.1 (2)°; Back *et al.*, 1998].

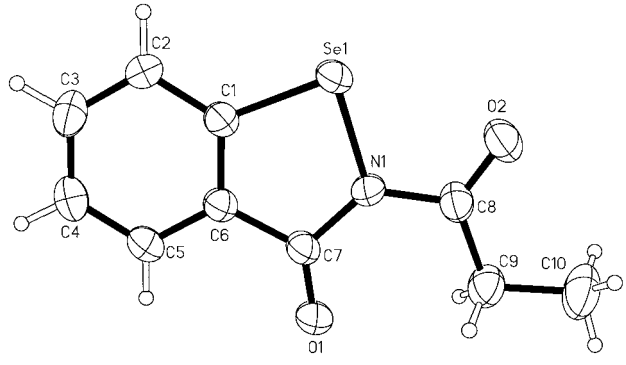



**Figure 1**
*ORTEP*II (Johnson, 1976) plot of (I) at the 50% probability level. H atoms are drawn as circles of arbitrary radii.

## Experimental

Elemental selenium was reduced by potassium borohydride and the product was treated with diazotized anthranilic acid to furnish 2,2′-diselenobis(benzoic acid), which was then converted to 2-chloroselenobenzoyl chloride (Kamigata *et al.*, 1986). This compound (2.0 g, 33 mmol) and urea (1.3 g, 5 mmol) were refluxed, under an atmosphere of nitrogen, in dry benzene (30 ml) overnight. The crude product was collected by filtration and then washed with 10% sodium bicarbonate. The dried material was recrystallized from ethanol to afford *N*-carbamoyl-1,2-benzisoselenazol-3(2*H*)-one (m.p. 483 K) in 70% yield. C, H and N analyses, found: C 39.56, H 2.70, N 11.88%; calculated for $C_8H_6N_2Se$: C 39.83, H 2.49, N 11.62%. $^1$H NMR (DMSO): 7.20–7.70 (*m*, 4H, Ar–H), 3.62 (*s*, 2H, $NH_2$) p.p.m. IR: 3373, 1701, 1624, 1575, 1325 cm$^{-1}$. MS: 242 ($M^+$ based on 80Se). A mixture of *N*-carbamoyl-1,2-benzisoselenazol-3(2*H*)-one (4 mmol), propionic acid (5 ml) and propionyl chloride (2 ml) was refluxed overnight. After cooling the reaction mixture, the liquid was removed by distillation under vacuum. The residue was extracted with ethyl acetate and the crude product was isolated by chromatography on silica gel/chloroform in 40% yield. Faint tan-colored crystals of *N*-propionyl-1,2-benzisoselenazol-3(2*H*)-one (m.p. 461 K), were obtained by the use of either chloroform or ethyl acetate as the solvent for crystallization. C, H and N analyses, found: C 47.11, H 3.68, N 5.69%; calculated for $C_{10}H_9NO_2Se$: C 47.24, H 3.54, N 5.51%. $^1$H NMR ($CDCl_3$): 7.40–8.05 (*m*, 4H, Ar–H), 1.10 (*t*, 3H, $CH_3$), 3.05 (*q*, 2H, $CH_2$) p.p.m. IR: 3132, 2974, 1658, 1595, 1400 cm$^{-1}$. MS: 255 ($M^+$).

Compound (I) can also be synthesized by the direct reaction of chloroselenobenzoyl chloride with acetamide (Mlochowski *et al.*, 1993). In the present synthesis, *N*-carbamoyl-1,2-benzisoselenazol-3(2*H*)-one, when reacted with the acyl chloride *R*COCl (*R* = $CH_3CH_2$), gave the title compound instead of the diacyl urea $C_6H_4C(O)N[C(O)NHC(O)R]Se$. This compound is probably formed in the reaction, but it then liberates formaldehyde to form (I). Such behavior is typical of diacyl ureas (Stoughton, 1938).

Geometry optimization was performed using the *GAUSSIAN*-94 suite (Frisch *et al.*, 1995). The geometry of the isolated molecule was initially optimized by the CNDO (complete neglect of differential overlap; Segal & Pople, 1966) method, and the resulting structure used as a starting point for further optimization at the Hartree–Fock self-consistent field level. The energy derivatives were computed analytically using Berny's algorithm (Schlegel, 1982). The calculations made use of the split-valence 3–21G basis set for medium-size molecules (Durig *et al.*, 1992). Mulliken population analysis (Mulliken, 1955) was used to estimate the partial charge distribution (Table 1). Similar calculations were also performed on the *N*-methyl and *N*-phenyl derivatives.

*Crystal data*

$C_{10}H_9NO_2Se$
$M_r$ = 254.14
Triclinic, $P\overline{1}$
$a$ = 6.8865 (2) Å
$b$ = 8.0840 (2) Å
$c$ = 9.8348 (1) Å
α = 70.542 (1)°
β = 75.896 (1)°
γ = 71.249 (1)°
$V$ = 483.08 (2) Å$^3$
$Z$ = 2
$D_x$ = 1.747 Mg m$^{-3}$
Mo $K\alpha$ radiation
Cell parameters from 2878 reflections
θ = 2.22–28.24°
μ = 3.857 mm$^{-1}$
$T$ = 298 (2) K
Parallelepiped, colorless
0.46 × 0.28 × 0.12 mm

*Data collection*

| | |
|---|---|
| Siemens CCD area-detector diffractometer | 2271 independent reflections |
| $\omega$ scans | 1964 reflections with $I > 2\sigma(I)$ |
| Absorption correction: empirical (*SADABS*; Sheldrick, 1996) | $R_{int} = 0.041$ |
| $T_{min} = 0.270$, $T_{max} = 0.655$ | $\theta_{max} = 28.24^\circ$ |
| 3461 measured reflections | $h = -8 \rightarrow 9$ |
| | $k = -10 \rightarrow 10$ |
| | $l = -7 \rightarrow 12$ |

*Refinement*

| | |
|---|---|
| Refinement on $F^2$ | H-atom parameters constrained |
| $R[F^2 > 2\sigma(F^2)] = 0.056$ | $w = 1/[\sigma^2(F_o^2) + (0.0996P)^2]$ where $P = (F_o^2 + 2F_c^2)/3$ |
| $wR(F^2) = 0.150$ | $(\Delta/\sigma)_{max} < 0.001$ |
| $S = 1.011$ | $\Delta\rho_{max} = 1.49$ e Å$^{-3}$ |
| 2271 reflections | $\Delta\rho_{min} = -1.59$ e Å$^{-3}$ |
| 127 parameters | |

**Table 1**
Relative Mulliken partial charges of the atoms of *N*-propionyl-1,2-benzisoselenazol-3(2*H*)-one and *N*-methyl-1,2-benzisoselenazol-3(2*H*)-one[a].

| Atom[b] | *N*-propionyl | *N*-methyl |
|---|---|---|
| Se1 | 0.913 | 0.851 |
| O1 | −0.634 | −0.658 |
| O2 | −0.611 | |
| N1 | −1.189 | −1.061 |
| C1 | −0.501 | −0.485 |
| C2 | 0.023 | 0.019 |
| C3 | 0.049 | 0.039 |
| C4 | 0.007 | 0.005 |
| C5 | 0.116 | 0.110 |
| C6 | −0.144 | −0.141 |
| C7 | 0.979 | 0.972 |
| C8 | 0.931 | 0.351 |
| C9 | −0.007 | |
| C10 | 0.069 | |

† Notes: (*a*) the charges of the H atoms were summed into the charges of the C atoms; (*b*) the atom-numbering scheme for the calculated structures uses the labels of the $C_7H_4NOSe$ entity in Fig. 1; C8 in the *N*-methyl derivative refers to the methyl C atom.

H atoms were treated as riding with $U(H) = 1.5U_{eq}(C)$. The maximum and minimum residual electron-density peaks are 0.92 and 0.79 Å, respectively, from the Se1 atom.

Data collection: *SMART* (Siemens, 1996); cell refinement: *SAINT* (Siemens, 1996); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS*97 (Sheldrick, 1997); program(s) used to refine structure: *SHELXL*97 (Sheldrick, 1997); molecular graphics: *ORTEP*II (Johnson, 1976); software used to prepare material for publication: *SHELXL*97.

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Supplementary data for this paper are available from the IUCr electronic archives (Reference: DE1150). Services for accessing these data are described at the back of the journal.

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