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Synthesis and Structures of Se Analogues of the Antithyroid Drug 6-*n*-Propyl-2-thiouracil and Its Alkyl Derivatives: Formation of Dimeric Se–Se Compounds and Deselenation Reactions of Charge-Transfer Adducts of Diiodine

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Abstract: Four selenium analogues of the antithyroid drug 6-*n*-propyl-2-thiouracil (PTU), of formulae RSeU, (R = methyl (Me) (**1**), ethyl (Et) (**2**), *n*-propyl (*n*Pr) (**3**), and isopropyl (*i*Pr) **4**), have been synthesized. Reaction of **1**–**4** with diiodine in a 1:1 molar ratio in dichloromethane results in the formation of [(RSeU)I_2] (R = methyl (**5**), ethyl (**6**), *n*-propyl (**7**) and isopropyl (**8**)). All compounds have been characterized by elemental analysis, FT-Raman, FT-IR, UV/Vis, ^{1}H–, ^{13}C–, ^{77}Se–1D and -2D NMR spectroscopy, and ESI-MS spectrometric techniques. Recrystallization of **4** from dichloromethane afforded (**4**·CH_2Cl_2). Crystals of [(*n*PrSeU)I_2] (**7**), a charge-transfer complex, were obtained from chloroform solutions, while crystallization of **6** and **7** from acetone afforded the diselenides [*N*-(6-Et-4-pyrimidone)(6-EtSeU)$_2$] (**9**·2H_2O) and [*N*-(6-*n*Pr-4-pyrimidone)(6-*n*PrSeU)$_2$] (**10**) as oxidation products. Recrystallization of **7** from methanol/acetonitrile solutions led to deselenation with the formation of 6-*n*-propyl-2-uracil (*n*PrU) (**11**). [(*n*PrSeU)I_2] (**7**) was found to be a charge-transfer complex with a Se–I bond. These results are discussed in relation to the mechanism of action of antithyroid drugs.

Keywords: bioinorganic chemistry · charge-transfer complexes · heterocyclic selenoamides · iodine adducts · selenium

Introduction

The first step in the action of the thyroid hormone has been shown to be monodeiodination of prohormone thyroxine (T_4) to the biologically active hormone 3,5,3′-triiodothyronine (T_3).[1] The mechanism of this deiodination reaction employs a selenocysteine-containing enzyme, iodothyronine deiodinase-I (ID-1), which is responsible for the removal of one iodine atom of thyroxine T_4 and its conversion to T_3.[1,2] The drugs most often used in the case of overproduction of T_3 (Graves' disease, hyperthyroidism) are *N*-methyl-2-mercapto-imidazole (MMI) and 6-*n*-propyl-2-thiouracil (PTU).[3] It has been proposed that PTU is more likely to act at the stage of the de-iodination of T_4 from ID-1 enzyme, by reacting with the intermediate ID-1-SeI, leading to a dead-end selenenyl sulfide ID-1-Se-S(PTU).[1,2] It has also been proposed that the selenium analogues of PTU, 6-*n*-propyl-selenouracil, (PSeU), might be a more potent inhibitor of ID-1 than PTU,[2a,4a] and it was estimated to be twice as potent as PTU in inhibiting ID-1 activity[4a] on account of the more facile formation of a Se–Se bond.[1c,2e,4] Selenium compounds are also known to be present in the thyroid gland in the form of selenocysteine in glutathione peroxidase GPx, an enzyme that degrades intracellular H_2O_2, which activates the thyroid peroxidase (TPO).[5]

Despite the fact that uncharged covalent selenium–iodine compounds were regarded as nonexistent for a long time,[6] the crystal structures of selenoether-iodine complexes were reported in the 1960s.[7] Organic selone and/or selenoamides are believed to act as donors towards diiodine and certain iodine compounds as charge-transfer complexes that are generally more stable than those of the corresponding sulfur compounds.[6b,8–12] Although, fully characterized uncharged covalent selenium–iodine (Se–I) compounds with two-center

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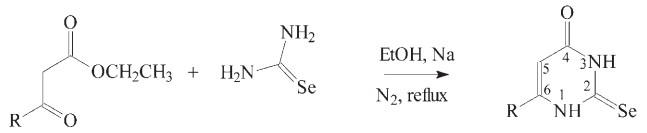
two-electron bonds are still extremely rare, the conditions for the formation of Se–I compounds are now well-understood.[6b,8–12] Reactions between selones or selenoamides with diiodine or interhalogens I–X (X = I, Br or Cl) lead to the formation of charge-transfer complexes[11] including: i) "spoke structures" or "extended spoke structures" bearing a linear arrangement of Se-I-X (X = I, Br or Cl) or Se-I-I···I–I groups, ii) two-coordinate iodine(I) cationic or iodonium salts with selone compounds ([LSe-X-SeL], iii) donor oxidation products, including dicationic diselenides $[LSe–SeL]^{2+}\cdot 2I_3^-$, or neutral diselenides, and iv) T-shaped compounds with a linear I-Se-X (X = I, Br or Cl) group.[5a,6b,8–12] Monocationic diselenide species have not yet been observed for selone–iodine interaction products.

To better understand selenium–I_2 chemistry and possibly draw conclusions concerning the higher potential activity of PSeU over PTU[4a,b] and their mechanism of action in general, four alkyl selenouracil derivatives were synthesized. We report herein reactions of these selone or selenoamides with I_2 to afford charge-transfer adducts and diselenide products. Diselenides are easily produced upon leaving selenium complexes of RSeU with I_2 to stand in acetone.

Results and Discussion

General aspects: Compounds **1**–**4** were synthesized as shown in Scheme 1.[4c] The crystal structures of compounds **1**–**4** and **4**·CH_2Cl_2 were determined by X-ray diffraction. These structures together with detailed structures of compounds **7**, **9**, **10**, and **11** are reported separately,[13] and only the relevant structural features are discussed in this paper.



Scheme 1. Alkyl selenouracil compounds synthesized. R = methyl (Me, **1**), ethyl (Et, **2**), *n*-propyl (*n*Pr, **3**), and isopropyl (*i*Pr, **4**).

Reaction of **1**–**4** with diiodine in a 1:1 molar ratio in dichloromethane solutions results in the formation of [(RSeU)I_2] (R = methyl (**5**), ethyl (**6**), *n*-propyl (**7**) and isopropyl (**8**)).

Spectroscopy:

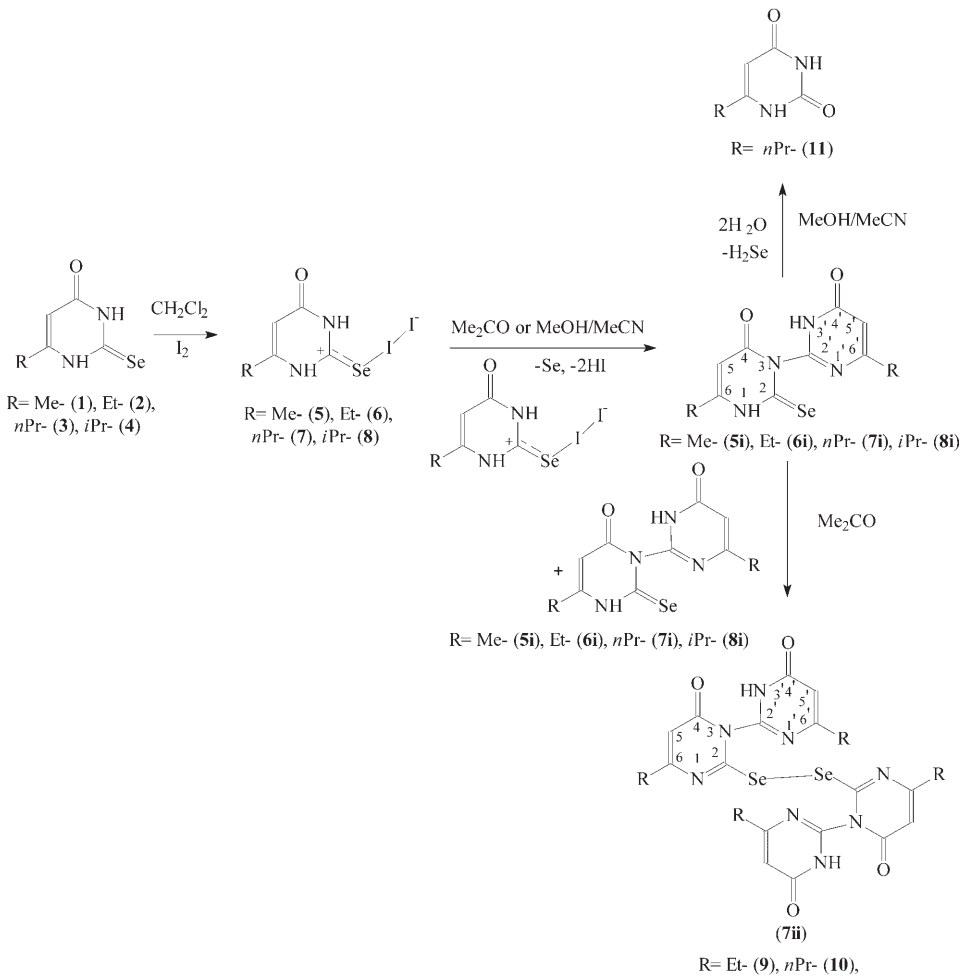
UV/Vis: The UV/Vis spectra of 6-alkyl-2-selenoamides **1**–**4** in dichloromethane show one absorption in the region of 310–312 nm (311 nm for **1**, 310 nm for **2**, 312 nm for **3**, and 310 nm for **4**) with ε values in the range of 5000–8000. These values, together with a shift to slightly higher wavelengths of the λ_{max} on going from dichloromethane to acetone and chloroform, indicate a $\pi^*\leftarrow$n transition. A second band at 231–233 nm is also observed in the UV/Vis spectra of 6-alkyl-2-selenoamides **1**–**4** in dichloromethane solutions (231 nm for **1**, 232 nm for **2**, 231 nm for **3**, and 233 nm for **4** (ε = 35000–40000)) red-shifted in chloroform that can be assigned to $\pi^*\leftarrow\pi$ transitions.

The visible spectra of the selenoamide–diiodine adducts in dichloromethane exhibit one distinct absorption band at 495–505 nm (at 501 nm for **5** and **6** and at 497 nm for **7** and **8**), which is assigned to the "blue-shift" band of I_2.[14] A shoulder in the range of 285–287 nm (at 286 nm for **5**, 285 nm for **6**, and at 287 nm for **7** and **8**) for these complexes can be assigned, based on literature examples, to a charge-transfer (CT) band from the HOMO of the donor to the diiodine LUMO (σ_π^*).[9a,15,16] According to an assumption by Laurence et al.,[16] CT absorption bands of I_2–thioamide complexes can be correlated with an in-plane or a perpendicular arrangement of the I_2 moiety towards the plane of N-C=S, and this hypothesis seems to apply to the selenoamide–I_2 adducts studied here. Thus, complexes of I_2–thioamide with in-plane conformation, where the X−C=S···I torsion angle was close to 0°, exhibit a CT band at 295–305 nm, while those with perpendicular arrangements with the angle near 90° displayed this band at about 320–350 nm.[16] Generally, in the case of thioamide–diiodine complexes, perpendicular arrangements are expected when the substituents around the thioamide group are bulky,[16] whereas a planar arrangement is expected when there is a NH group *cis* to the thione group.[16] Therefore, coplanar arrangements are expected for all our complexes because they all contain a *cis*-NH group that is able to form a hydrogen bond to I_2. This is confirmed in the case of compound **7** where the I-Se-C-N torsion angle is −0.45° (see the crystal structure below). Because complex **7** also shows a CT band at 287 nm, the CT bands that appear in the region of 285–287 nm for complexes **5**–**8** should be assigned to a coplanar arrangement of the N-C=Se group with I_2. The wavelength values of CT bands for the torsion angles in a perpendicular arrangement are unknown at present for the selenoamide–I_2 complexes because no such crystal structure has been determined thus far.

The absorption bands at 308–315 nm, as well as the bands at 226–228 nm in the spectra of complexes **5**–**8**, are attributed to intraligand ($\pi^*\leftarrow\pi$) transitions because they are also present at the same wavelength for the free ligand.

^1H NMR: ^{1}H NMR spectroscopy provides good indications for the formation of one intermediate product **7i** on leaving a acetone or methanol solution of complex **7** [(PSeU)I_2] to stand (Scheme 2). This forms a final diselenide **7ii** in acetone and *n*Pr-Uracil in methanol.

Thus, ligand **3** (PSeU) shows one signal at δ = 5.84 ppm, assigned to H5 of selenouracil ring in $(CD_3)_2CO$. This shifts to δ = 5.96 ppm in complex **7**. One hour later, a new band appears at δ = 6.43 ppm, which can be assigned to H5′, with H5 coinciding with the starting complex resonance at δ = 5.96 ppm of the intermediate product **7i** (Scheme 2). A black precipitate starts appearing simultaneously in the ^{1}H NMR tube, which is elemental Se. A second species ap-



Scheme 2.

pears in the ^{1}H NMR spectra after leaving for 12 h in the same solvent. This species exhibits two resonance at δ = 6.31 and 5.88 ppm assigned to H5′ and H5 of a new diselenide species, namely **7ii**.

The resonance at δ = 6.38 ppm, assigned to **7i**, disappears completely after about 48 h. At this stage, the relative intensity of H5′ of **7ii** at δ = 6.30 ppm with respect to H5 of **7** at δ = 5.87 ppm is 0.35. On the other hand, in (CD_3OD) solutions, the H5 signal of ligand **3** is at δ = 5.88 ppm. Two bands appear for complex **7** at δ = 6.47 and 5.97 ppm assigned to H5′ and H5 of intermediate **7I**, which, however, end up in compound **11** *n*Pr-Uracil, in which C=Se is replaced by a C=O bond following hydrolysis of the N3–C2′ bond of **7i**. Further ^{1}H NMR peaks of all compounds are reported in the Experimental Section.

^{13}C NMR: The ^{13}C NMR spectrum of ligand **3** exhibits the following signals: δ = 105.2 (C5), 157.6 (C6), 160.9 (C4), and 176.2 ppm (C2 bonded to Se); the assignments were revealed by an HMBC experiment.

Product **7ii** exhibits signals at δ = 106.7 (C5), 154.3 (C6), 198.2 (C4), and 125.1 ppm (C2). The corresponding signals for C5′, C6′, C4′, and C2′ appear at 106.7, 157.9 210.1, and 160.7 ppm, respectively.[17a] Further ^{13}C NMR peaks of all compounds are reported in the Experimental Section.

^{77}Se NMR: The ^{77}Se NMR spectra of compounds MeSeU (**1**), EtSeU (**2**), and *n*PrSeU (**3**) in [D_6]DMSO each show a single resonance with a chemical shift at δ = 321.8, 322.1, and 325 ppm, respectively, assigned to the unique Se nuclei of the molecules. The ^{77}Se NMR spectra of complexes [MeSeU)I_2] (**5**), [EtSeU)I_2] (**6**), and [(*n*PrSeU)I_2] (**7**) in $(CD_3)_2CO$ show resonance signals with chemical shifts at δ = 361.3 (**5**), 362 (**6**), and at 362.4 (low intensity) and 358.7 ppm (strong) (**7**), which can be assigned to the ^{77}Se nucleus of the (RSeU)I_2 complex. For all compounds, the second strong signal observed near δ = 358.0 ppm is probably attributable to the intermediates **7i** that result when their deuterated acetone solutions are left to stand for more than 1 h.

ESI-MS: The ESI-MS spectra of compounds **1**–**4** show peaks centered at *m*/*z* 191 for $[MeSeU{\cdot}H]^+$ (**1**), at *m*/*z* 205 for $[EtSeU{\cdot}H]^+$ (**2**), at *m*/*z* 219 for $[n$PrSeU$\cdot$H$]^+$ (**3**) and at *m*/*z* 219 $[i$PrSeU$\cdot$H$]^+$ (**4**), which are attributed to their molecular ions.

Owing to the cleavage of the C–Se bond observed in methanolic solutions (see crystal structures below), the ESI-MS spectra (of freshly prepared solutions in 1/1 MeOH/H_2O) of complexes **5**–**8** contain several fragments. Thus fragments observed at *m*/*z* 297, 325, 353, and 353 are attributed to the cations $[C_{10}H_{10}N_4O_2Se]^+$ in the case of **5i**, $[C_{12}H_{14}N_4O_2Se]^+$ for **6i** and to $[C_{14}H_{18}N_4O_2Se]^+$ for **7i** and **8i**, respectively, which may be formed by the *N* substitutions of RSeU by 6-R-4-pyrimidone (Scheme 2).

Vibrational spectroscopy: Characteristic IR bands of the complexes and their compounds are listed in Table 1.

The vibrational spectra of complexes (RSeU)I_2 show distinct bands at 1547–1557 and 1388–1399 cm^{-1}, which can be assigned to $\nu_s(N_2CSe)$ and δ(NCSe) vibrations.[17b] The corresponding bands observed for the free compounds **1**–**4** are at 1542–1552 cm^{-1} and 1378–1399 cm^{-1}, respectively. These bands shift upon coordination ($(\nu_s(N_2CSe)$: 5 cm^{-1} (**5**) and 15 cm^{-1} (**7**)), while δ(NCSe) shifts by 10 (**5**), −11 (**6**), 10 (**7**),

Table 1. Characteristic vibration bands in the IR and Raman spectra of complexes **5**–**8** and/or compounds **1**–**4**.

Compound	IR [cm^{-1}]			Raman [cm^{-1}]
	ν_{as}(C=O)	ν_s(N_2CSe)	δ(NCSe)	
1	1634	1552	1378	
2	1660	1552	1399	
3	1660	1541	1383	
4	1655	1547	1383	
5	1680	1557	1388	211 s, 234 vs
6	1639	1552	1388	216 s, 232 vs
7	1685	1557	1393	214 s, 232 vs, 264 br, 299 br
8	1685	1547	1399	206 sh, 234 vs

and 16 cm^{-1} (**8**)). The ν(CO) bands are observed in the IR spectra of the complexes in the 1639–1685 cm^{-1} region and shift to higher wavenumbers compared to the corresponding bands observed for the free compounds **1**–**4** (46 (**5**), 25 (**7**), 30 cm^{-1} (**8**)] upon coordination to I_2, while in case of **6** the ν(CO) are shifted to lower wavenumbers (21 cm^{-1}).

The characteristic Raman frequencies of the compounds are also included in Table 1. Diiodine vapor gives a strong ν(I–I) band at 216 cm^{-1}, which appears at 180 cm^{-1} in the solid state.[9c,17c] This band shifts to lower wavenumbers upon coordination to a donor atom, reflecting the reduction in the I–I bond order and the subsequent strengthening of the Se–I bond being formed.[11a,b] The Raman spectra of complexes **5**–**8**, recorded in the 300–50 cm^{-1} region, show a strong band at 206–216 cm^{-1}, very close to that reported for a diiodine vapor.[9c] It is presumably attributable to the partial loss of iodine from the complexes. It might also be attributable to the stretching of Se–Se bonds.[11d] A second, very strong band in the Raman spectra of complexes recorded at 232–234 cm^{-1} is assigned to the C-Se-I bending mode.[11f]

Recrystallization of powered alkylselenouracils **1**–**4** from water gave crystals suitable for an X-ray diffraction study. To investigate the influence of solvent on the extended structures formed by the alkylselenouracils, **4** was also recrystallized from dichloromethane as the 1:1 adduct **4**·CH_2Cl_2. ORTEP diagrams and selected bond lengths and angles of **1**–**4** and **4**·CH_2Cl_2 are shown in Figures 1–5, respectively.

The molecular structures of the alkylselenouracils are unremarkable.[13] Furthermore, the molecular structure of **4** is not affected by recrystallisation from dichloromethane as **4**·CH_2Cl_2. The C–Se bond lengths in **1**–**4** and in **4**·CH_2Cl_2 vary from 1.824(2) to 1.848(6) Å, indicating a double bond character.[9b] The free ligands do not undergo any change upon recrystallization in polar (aqueous) solvents.

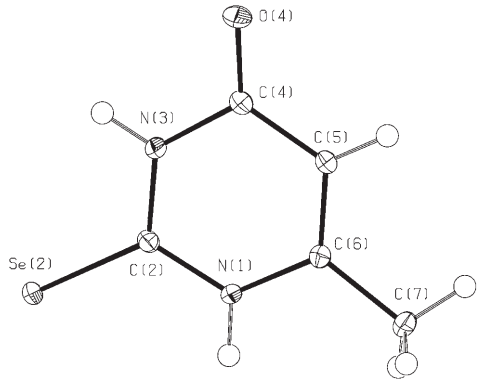


Figure 1. ORTEP diagram of compound **1**. Selected bond lengths [Å] and angles [°]: Se(2)–C(2) 1.832(2), O(4)–C(4) 1.233(3), Se(2)-C(2)-N(3) 121.99(16).

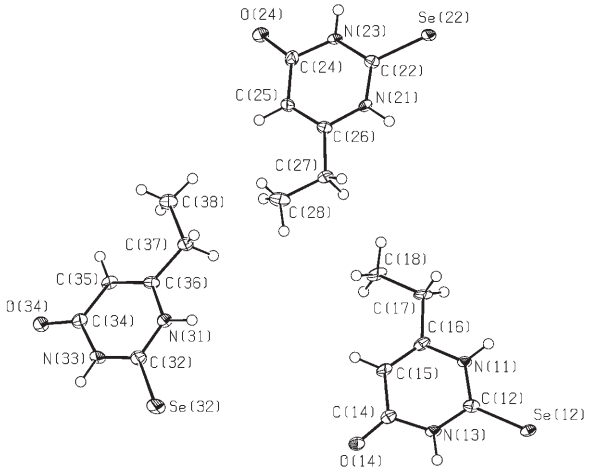


Figure 2. ORTEP diagram of compound **2**. There are three independent molecules in the asymmetric unit. Selected bond lengths [Å] and angles [°]: Se(12)–C(12) 1.835(6), Se(22)–C(22) 1.848(6), Se(32)–C(32) 1.828(7), O(14)–C(14) 1.240(8), O(24)–C(24) 1.242(8), O(34)–C(34) 1.227(7); Se(12)-C(12)-N(13) 121.5(4), Se(22)-C(22)-N(23) 122.8(4), Se(32)-C(32)-N(33) 121.2(5).

Compound **7** (Figure 6) exhibits the so-called "spoke" structure.[18] There are only a few crystal structures reported in the literature that contain the C=Se–I–I group.[11a,d,19]

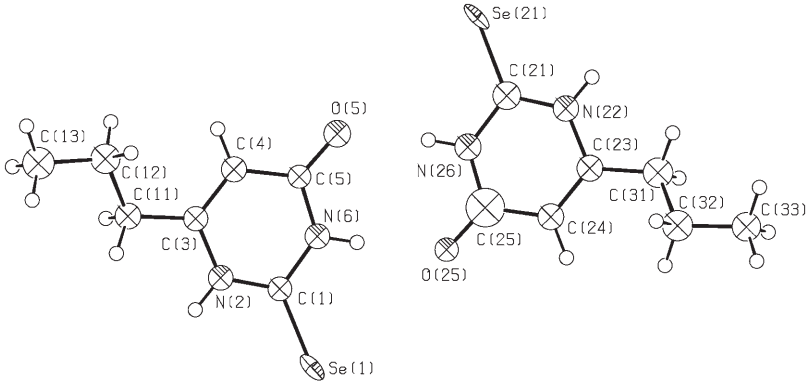


Figure 3. ORTEP diagram of compound **3**. There are two independent molecules in the asymmetric unit. Selected bond lengths [Å] and angles [°]: Se(1)–C(1) 1.837(16), Se(21)–C(21) 1.835(16), O(5)–C(5) 1.23(2), O(25)–C(25) 1.24(2); Se(1)-C(1)-N(6) 121.7(12), Se(1)-C(1)-N(6) 121.7(12).

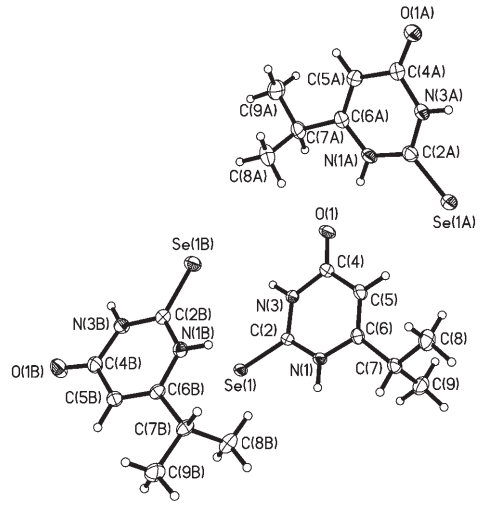


Figure 4. ORTEP diagram of compound **4**. There are three independent molecules in the asymmetric unit. Selected bond lengths [Å] and angles [°]: Se(12)–C(12) 1.850(4), Se(22)–C(22) 1.827(5), Se(32)–C(32) 1.835(4), O(14)–C(14) 1.230(5), O(24)–C(24) 1.228(7), O(34)–C(34) 1.227(7); Se(12)-C(12)-N(11) 120.6(3), Se(22)-C(22)-N(21) 123.8(3), Se(32)-C(32)-N(31) 122.9(3).

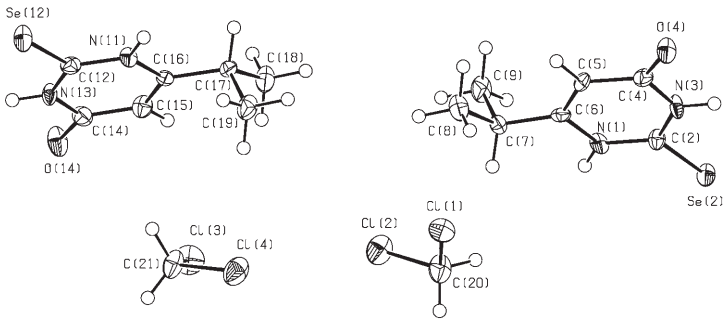


Figure 5. ORTEP diagram of compound **4**·CH_2Cl_2. There are two independent molecules of **4** in the asymmetric unit, solvated by two dichloromethane molecules. Selected bond lengths [Å] and angles [°]: Se(2)–C(2) 1.829(6), Se(12)–C(12) 1.825(5), O(4)–C(4) 1.232(7), O(14)–C(14) 1.233(7); Se(2)-C(2)-N(1) 123.0(4), Se(12)-C(12)-N(11) 123.5(4).

These include (tzSeMe)·I_2 (tzSeMe = *N*-methylthiazolidine-2(3*H*)-selone,[11a] (btSeMe)·2I_2 (btSeMe = *N*-methyl-benzothiazole-2(3*H*)-selone,[11a] [(L·I_2)·$(L_2)^+$·2I_3^-](L = bis(*N*,*N*′-dimethyl-imidazolidin-2-yl)diselenone)[11d] and (mbis)·2I_2 (mbis = 1,1′-bis(3-methyl-4-imidazolin-2-selenone)methane).[20] Complex **7** consists of a selenoamide ligand bonded with a diiodine molecule through selenium, with Se–I = 2.7807(11) Å, (Figure 6). This bond length is the longest ever measured and indicates a weak interaction (Table 2).

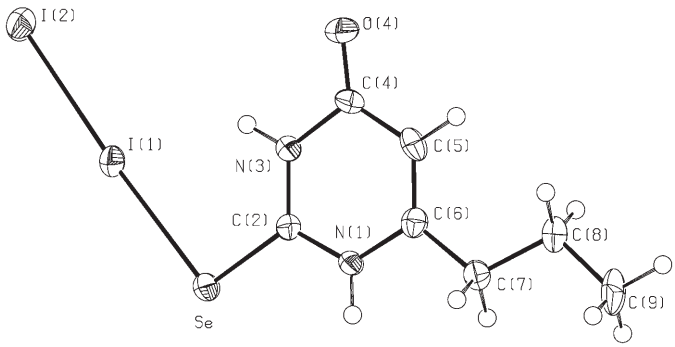


Figure 6. ORTEP diagram of complex **7**. Selected bond lengths [Å] and angles [°]: I(1)–I(2) 2.8928(10), I(1)–Se 2.7807(11), Se–C(2) 1.876(6), O(4)–C(4) 1.213(8); I(2)-I(1)-Se 176.75(2), I(1)-Se-C(2) 96.9(2).

The C–Se bond length of **7** (Se–C(2) = 1.876(6) Å) (Figure 6) is significantly longer than that of the corresponding free ligand *n*PrSeU (**3**) (average C–Se bond lengths 1.836(11) Å, Figure 3), owing to its coordination to diiodine, but it is similar to the C–Se bond lengths found for selenoamide–diiodine CT complexes with spoke structures (Table 2).

The corresponding I–I bond lengths are longer with values of I–I = 2.8928(10) Å in **7** (Figure 6), as compared to the I–I distances either in the gas phase (2.677 Å),[14b,21a] or in crystalline diiodine (2.717 Å at 110 K),[14b,21b] as a result of the Se···I interaction. However, the I–I bond length found in **7** is the shortest such distance measured in diiodine–selenoamide complexes (Table 2), consistent with the previously discussed weak Se···I interaction.

The I–I bond order of compound **7** is calculated to be 0.547, according to Pauling's equation[21a] and can be classified as type B according to Bigoli et al.[15a,b]

Table 2. Bond lengths [Å], bond angles [°], and other structural parameters of known iodine complexes.

Compound	Se–I [Å]	C=Se [Å]	I–I bond coord [Å]	Bond order [e][a]	Se-I-I [°]	X-C-Se-I torsion [°]	Ref.
[{(*n*PrSeU)I_2}·I_2] (**7**)	2.7807	1.8757	2.8927	0.547	176.75	−0.45 X = N3	[b]
						−179.31 X = N1	
(tzSeMe)·I_2[c]	2.726(1)	1.877(8)	2.983(1)	0.428	177.49(3)	172.16 X = N1	[11a]
						−12.04 X = S1	
(btSeMe)·2I_2[c]	2.639(1)	1.853(8)	3.071(1)	0.337	176.66(3)	172.99 X = N1	[11a]
						−7.26 X = S1	
{(L·I_2)·$(L_2)^+$·2I_3^-}[c]	2.683(1)	1.8825	3.025(1)	0.382	175.52	72.99 X = N6	[11d]
						−105.06 X = N3	
(mbis)·2I_2[c]	2.776(1)	1.879	2.912(1)	0.519	176.86(4)	−100.15 X = N1	[19]
	2.716(2)	1.858	2.995(1)	0.415	175.63(4)	81.75 X = N2	
						−100.32 X = N3	
						84.58 X = N4	

[a] Calculated in this work. [b] This work. [c] tzSeMe = *N*-methylthiazolidine-2(3*H*)-selone, btSeMe = *N*-methylbenzothiazole-2(3*H*)-selone, L = bis(*N*,*N*′-dimethylimidazolidin-2-yl)diselenone, mbis = 1,1′-bis(3-methyl-4-imidazolin-2-selenone)methane

For selenium "spoke" structure complexes, such as **7**, there is a linear correlation between the Se–I and I–I distances [Eq. (1)].

$$d(\mathrm{Se{-}I}) = -0.7981\,d(\mathrm{I{-}I}) + 5.0983\;R^2 = 0.9805 \qquad (1)$$

Given that the I–I interatomic distance for free diiodine in the solid state is (2.717 Å),[14b,21b] the longest possible Se–I interatomic distance calculated from Equation (1) is 2.93 Å. Thus, the value of 2.7807 Å for **7** suggests a relatively weak interaction between selenium and iodine.

The I1-Se-C2-N3 or I1-Se-C2-N1 torsion angles for compound **7** are −0.5(6)° or −179.3(5)°, respectively, which confirm the coplanar arrangement of I–I with respect to the C=Se group as predicted by UV/Vis spectroscopy.[15] Finally, the values for the Se-I-I angles also imply an almost linear arrangement, as expected for CT complexes with a "spoke" structure.

Recrystallization of **7** in MeCN/MeOH (1/1) solutions results in the formation of compound **11**, according to the reaction shown in Scheme 2.

The two C=O bond lengths found for **11** are almost equal (O(2)–C(2) 1.2285(13) and O(4)–C(4) 1.2387(15) Å, respectively) (Figure 7) and are within the range of the C–O bonds found for similar compounds, such as 1,3,6-trisubstituted uracils (1,3-Me-6-R-2-U) (C1–O(1) 1.233(3) (R = Me), 1.224(2) (R = Et), 1.212(3), 1.221(3), 1.220(3) (R = *n*Pr), and 1.220(5) 1.226(5) (R = *n*Bu),[22a] Triethylammonium 2,4-dioxo-6-(1,1,2,2,3,3-hexafluoropropyl)-5-benzylsulfonyl-3*H*-2,4-dihydropyrimidine[22b] (C(2)–O(1) 1.235(3) and C(4)–O(2) 1.237(2) Å).

Recrystallization of **6** and **7** from Me_2CO solutions results in the formation of the diselenide compounds **9** and **10** (Scheme 2). Each is a selenoamide ligand that has been N-substituted by a deselenided molecule. Two such moieties are bonded through a Se–Se bond to form the corresponding diselenide. Table 3 compares the structural parameters of compounds **9** and **10** with other compounds of similar structure.

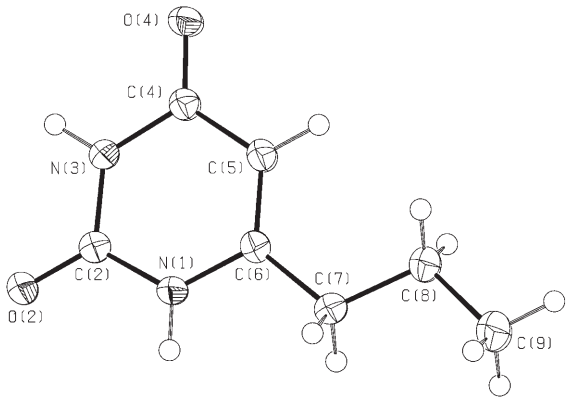


Figure 7. ORTEP diagram of molecule **11**. Selected bond lengths [Å] and angles [°]: O(2)–C(2) 1.2285(13), O(4)–C(4) 1.2387(15), N(1)–C(2) 1.3668(15), N(3)–C(2) 1.3653(14); O(2)-C(2)-N(3) 122.39(11), O(4)-C(4)-N(3) 119.56(11), O(4)-C(4)-C(5) 125.10(9).

The Se–Se bond lengths found in **9** and **10** are 2.428(2) and 2.4427(6) Å, respectively, and they are in the range of other diselenoamides (2.34–2.59 Å) (Table 3).

The C–Se bond lengths in **9** and **10** (1.925(4) and 1.922(4) Å, respectively (Figure 8 and Figure 9)) are longer than those of the corresponding free ligands EtSeU (**2**) and *n*PrSeU (**3**) (average C–Se bond lengths 1.837 and 1.8404 Å, respectively), owing to the dimerization (Table 3). The C–Se bond lengths found in **9** and **10** are in the range of other such compounds (1.874–1.952 Å) (Table 3). Compounds **9** and **10** are neutral diselenoamides with two unequal C–N

Table 3. Bond lengths [Å], bond angles [°], and other structural parameters of known diselenoamides.

Compound	Se–Se [Å]	C–Se [Å]	C–N [Å]	Se-Se-C [°]	C-Se-Se-C torsion [°]	Ref.
9	2.428(2)	1.925(4)	1.283(6), 1.412(6)	88.99(14)	−179.98(18)	[a]
10	2.4427(6)	1.922(4)	1.296(4), 1.407(4)	89.44(8)	180.00(14)	[a]
16	2.5188(7)	1.911(5)	1.310(5), 1.312(5)	89.22(12),96.76(13)	−84.25(19)	[22a]
		1.895(4)	1.312(6), 1.319(6)			
$\{(L{\cdot}I_2){\cdot}(L_2)^{+}{\cdot}2\,I_3^{-}\}$[b]	2.3715(14)	1.917(6)	1.308(8), 1.300(9)	95.2(2) 95.2(2)	82.4(3)	[11d]
		1.916(6)	1.295(9), 1.311(8)			
17	2.5970	1.9211	1.3049, 1.3067	96.24	77.63	[22b]
	2.7171	1.9400	1.3152, 1.2850	89.27	−80.49	
		1.9053	1.3101, 1.2953			
18	2.3447(11)	1.952(6)	1.316(8)	93.69(18)	−180.0(3)	[22c]
19	2.3568(14)	1.880(3)	1.319(4), 1.360(5)	99.45(12)	−64.20(15)	[22d]
20	2.4003(4)	1.874(2)	1.374(4)	98.33(8)	−50.67(13)	[22d]
21	2.409(2)	1.874(10)	1.332(12), 1.365(13)	95.7(3)	66.5(4)	[22e]
		1.874(11)	1.336(15), 1.362(14)			
22	2.434(2)	1.879(9)	1.329(13), 1.336(12)	96.0(3)	67.6(4)	[22e]
		1.881(10)	1.340(14), 1.331(13)	98.3(3)		
23	2.416(2)	1.900(5)	1.362(7), 1.326(8)	96.07(18)	93.1(3)	[22e]
		1.887(6)	1.349(8), 1.346(8)	98.91(17)		

[a] This work. [b] **16** = bis(*Se*,*Se*′-bis(*N*,*N*′-dimethylimidazolidin-2-ylidene)diselenium) bis(*N*,*N*′-dimethylimidazolidine-2 selone) heptakis(7,7,8,8-tetracyanoquinodimethane), L = bis(*N*,*N*′-dimethylimidazolidin-2-yl)diselenone, **17** = tris(selenourea) dichloride monohydrate, **18** = *N*,*N*,*N*′,*N*′-tetraethylthiuramdiselenide, **19** = bis(1-methylimidazol-2-yl)diselenide, **20** = bis(2-(4-bromophenyl)-4-(4-nitrophenyl)imidazol-5-yl)diselenide dimethylformamide solvate, **21** = *Se*,*Se*′-bis(1,3-dimethyl-4-imidazolin-2-yl)diselenium dibromide, **22** = *Se*,*Se*′-bis(1,3-Dimethyl-4-imidazolin-2-yl)diselenium diiodide, **23** = perhydro(1,2-*a*)(2,1-*e*)bis(3-methylimidazo)-3,4-diselena-1,6-diazocine triiodide tetraiodide.

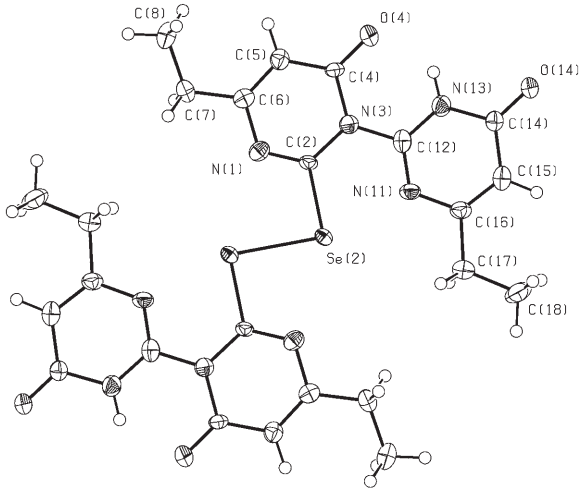


Figure 8. ORTEP diagram of molecule **9**. Selected bond lengths [Å] and angles [°]: Se(2)–Se(2a) 2.428(2), Se(2)–C(2) 1.925(4), O(4)–C(4) 1.233(5), N(3)–C(12) 1.420(5), O(14)–C(14) 1.232(3), N(11)–C(12) 1.296(4), N(13)–C(12) 1.337(3); Se(2a)-Se(2)-C(2) 88.99(14), C(2)-Se(2)-Se(2)-C(2a) –179.98(18).

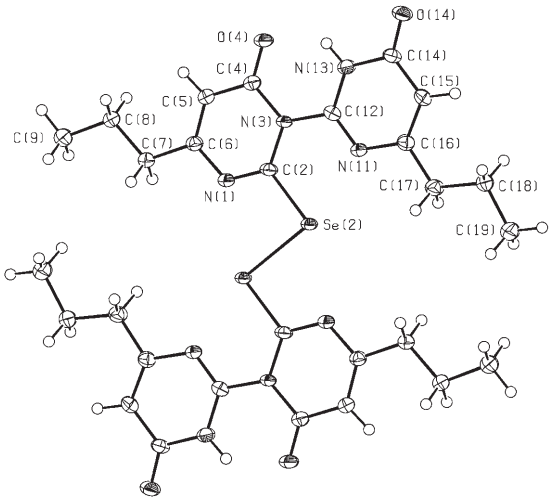


Figure 9. ORTEP diagram of molecule **10**. Selected bond lengths [Å] and angles [°]: Se(2)–Se(2a) 2.4427(6), Se(2)–C(2) 1.922(4), O(4)–C(4) 1.236(4), N(3)–C(12) 1.436(4), N(11)–C(12) 1.271(4), N(13)–C(12) 1.356(4), O(14)–C(14) 1.230(4); Se(2a)-Se(2)-C(2) 89.44(8), C(2)-Se(2)-Se(2a)-C(2a) 180.00(14).

bond lengths (1.283(6), 1.312(6) and 1.296(4), 1.407(4) Å, respectively, as expected for such compounds (Table 3, compound (**19**): C–N 1.319(4), 1.360(5) Å). The bond lengths become equal in the case of ionic diselenoamides (Table 3).

The measured Se-Se-C bond angles in compounds **9** and **10** are 88.99(14) and 89.44(8)°, respectively, and are independent of the molecular formula. The Se-Se-C bond angles of known deselenides vary between 89 and 99° (Table 3). The C-Se-Se-C torsion angles in compounds **9** and **10** are exactly 180° by symmetry, indicating a coplanar arrangement. This torsion angle varies between 180, 90, and 60° in all cases (Table 3).

Conclusions

Scheme 2 summarizes the reactions involved in the formation of compounds **5**–**11**. While 6-alkyl-2-selenouracil compounds (RSeU) (Scheme 2, **1**–**4**) are stable in various solvents, including water and other polar or nonpolar solvents, "spoke"-like CT complexes of formulae $[(RSeU)I_2]$ are formed in dichloromethane solutions; however, they are unstable in methanol/acetonitrile and/or acetone solutions (Scheme 2). $[(RSeU)I_2]$ is transformed to 6-alkyl-2-uracil in methanolic/acetonitrile solutions (Scheme 2). Upon recrystallization of the compound in acetone, the diselenides are formed possibly through the formation of a substituted selenouracil, as indicated by ^1H and ^{13}C NMR spectra as well as ESI-MS spectra. The whole process may be hydrolytic (Scheme 2).

The discovery that ID-l contains selenocysteine at its active site[1a] raised the possibility that the seleno analogues of *N*-methyl-2-mercapto-imidazole (MMI) and 6-*n*-propyl-2-thiouracil (PTU) might be better inhibitors of ID-1 than their respective parent compounds because they are expected to form an enzyme-Se-Se-drug adduct more readily than the corresponding enzyme-Se-S-drug complex. Viser et al.[4a] have shown that 6-*n*-propyl-2-selenouracil (PSeU) strongly inhibits enzyme ID-1, being twice as potent as PTU. However, Taurog et al.[4b] reported an almost equal inhibitory action of ID-1 by both PTU and PSeU and no activity of the selenoanalogue (MSeI) of MMI (*N*-methyl-2-seleno-imidazole) and MMI itself. This may be explained by the existence of MSeI as a diselenide,[5a] while PSeU is in its selone form.

Mugesh et al[5a,b] reported that the inhibition of lactoperoxidase (LPO) by MMI is more facile than that of its selenium analogue MSeI and the mechanism for the inhibition of LPO by MMI is different from that of MSeI. They also reported that MSeI, similarly to the sulfur analogue MMI, cannot inhibit ID-1, probably because of its inability to form a stable –Se–Se- bond with the active site of the enzyme.[5a] However, MSeI has been shown to exhibit high GPx activity, leading to the assumption that the selenium analogues of antithyroid drugs may have significant antioxidant activity in the thyroid gland.[5a,b]

Taurog et al.[4b] also compared both antithyroid drugs PTU and MMI with respect to their ability to inhibit ID-1. They concluded that the methyl substituent on the N atom of MMI or MSeI may be involved in the inhibitory action by preventing the formation of a hydrogen bond between the H(N) of the drug and the active site of the enzyme. This is further supported by the observation that *N*-methyl-6-*n*-propyl-2-thiouracil (NMPTU) does not show ID-1 inhibitory activity at all, while 2-mercaptoimidazole (MMI lacking the *N*-methyl substituent) has substantial ID-1 inhibitory activity. Therefore, Taurog et al.[4b] proposed that the ID-1 deiodinase inhibitory mechanism of selenoamides, similar to 6-*n*-propyl-2-selenouracil (PSeU), should not only be based on the greater propensity of PSeU to form the enzyme-Se-Se-PSeU adduct compared to its sulfur analogue PTU, but also

on the ability of the H(N) atom of PSeU to participate in a hydrogen bond with the active site of the enzyme.

Our findings show that the complexes of 6-*n*-propyl-2-selenouracil (PSeU) and all its alkyl derivatives with diiodine readily convert into [{*N*-(6-*n*Pr-PM)(6-R-SeU)}$_2$] iselenides (Scheme 2, **10**) in acetone or to 6-Pr-U (Scheme 2, **11**) in methanol, which are the final products. This may support the previous conclusions made by Visser[4a] and Taurog[4b] for the possible formation of stable –Se–Se- bonds, among other factors, to explain the ID-1 deiodinase activity of PTU and PSeU. Obviously, more work is required for any definitive conclusion to be made. The relative instability of the –Se–Se- bond, observed with MSeI, must also be taken in to account.[5a]

Experimental Section

Materials and instruments: All solvents used were of a reagent grade. Absolute ethanol, diiodine, and selenourea were obtained from Sigma-Aldrich. Ethyl acetoacetate, ethyl propionyl acetate, ethyl butyrylacetate, ethyl isobutyrylacetate, and ethylbenzoylacetate were purchased from Lancaster Chemicals Co. and were used without further purification. Elemental analyses for C, H, N were carried out with an Exeter Analytical Inc. CE-440 Elemental Analyser. Elemental analysis for iodine was carried out by means of the Schoniger oxygen flask method that employs Leipert titration.[23] Melting points were measured in open tubes on a Gallenkamp MF-370 melting point apparatus and are uncorrected. IR spectra in the 4000–370 cm^{-1} region were obtained as KBr discs with a Nicolet Avatar 360 FTIR spectrometer. A Perkin-Elmer Lambda 5 UV/Vis spectrophotometer was used to measure the electronic absorption spectra. Mass spectrometry measurements were performed on a Micromass LCT instrument. NMR spectra were recorded on Bruker Avance spectrometers operating at proton frequencies of 250.13 and 400.13 MHz and equipped with 5-mm multinuclear inverse probes with *z* gradients. Samples were prepared in [D$_6$]acetone (99.96%) and all experiments were performed at 298.0 K. Chemical shifts are given relative to solvent signals at δ = 2.05 ppm for ^{1}H and δ = 29.8 ppm for ^{13}C. Proton decoupling, achieved with the WALT-16 scheme, and ^{13}C spectra were recorded with a 30° flip angle. Gradient-selective 2D ^{1}H{^{13}C} HMQC and HMBC experiments were performed with and without decoupling, respectively.

Synthesis of compounds 1–4: All reactions and manipulations were carried out in dry ethanol, under nitrogen, in the dark using Schlenk techniques. 6-Methyl-2-selenouracil (MeSeU, **1**) and 6-*n*-propyl-2-selenouracil (*n*PrSeU, **3**) were synthesized according to the method described by Visser et al.,[4a] Taurog et al.,[4b] and Hu et al.[4c] The same method was used for the synthesis of compounds **2** and **4** (Scheme 1). Sodium metal (0.48 g, 0.02 mol) was dissolved in anhydrous ethanol (10 mL) and selenourea (1.72 g, 0.014 mol) and 0.01 mol of the appropriate 8-oxo ester (1.33 g ethyl acetoacetate for **1**, 1.44 g ethyl propionylacetate for **2**, 1.582 g ethyl butyrylacetate for **3**, and 1.58 g ethyl isobutyrylacetate for **4**) were added to the clear solution. The mixture was heated under reflux to yield a clear solution in about 10 min. Shortly afterwards, a precipitate began to form that did not change greatly in appearance after 2 h. After a total heating time of 6–7 h, the mixture was allowed to stand overnight. The solvent was removed in vacuo at 40–50° to near dryness and the residue was dissolved in water (10 mL). The product was precipitated by the addition of concentrated hydrochloric acid (1.4 cm^3) and subsequent acidification to pH 4 with glacial acetic acid. The 6-alkyl-seleno-2-uracil was filtered off, washed, and dried. Recrystallization of the resulting powders from water gave colorless crystals of compounds **1–4** that were suitable for X-ray single-crystal analysis, while recrystallization of **4** from dichloromethane gave crystals of **4**·CH$_2$Cl$_2$.[13] Crystals of the compounds were stored in the dark under N$_2$. They were found to be highly soluble in DMSO and hot water.

*MeSeU (**1**)*: $C_5H_6N_2OSe$; yield: 60%; m.p. >250°C; elemental analysis calcd (%): C 31.76, H 3.20, N 14.82; found: C 30.93, H 2.92, N 14.81; MS: *m*/*z*: 187; IR (KBr): $\tilde{\nu}$ = 3554 w, 3483 w, 3416 w, 3088 m, 2930 m, 2884 m, 1680 s, 1634 vs, 1552 vs, 1419 vs, 1378 m, 1347 s, 1235 m, 1189 s, 1148 vs, 1025 w, 958 w, 881 m, 846 s, 805 m, 584 s, 538 m, 508 s cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 5.93 (s, H5), 2.2 (s, 3H, H7), 1.151–1.149 ppm (d); ^{13}C NMR ([D$_6$]DMSO): δ = 174.125, 161.213, 153.255, 106.588, 19.334 ppm; ^{77}Se NMR ([D$_6$]DMSO): δ = 321.8 ppm; UV/Vis (CH_2Cl_2): λ (log ε) = 311 nm (4.0), 231 nm (4.38).

*EtSeU (**2**)*: $C_6H_8N_2OSe$; yield: 75%; m.p. 219–224°C; elemental analysis calcd (%): C 35.48, H 3.97, N 13.79; found: C 34.95, H 4.24, N 13.59; MS: *m*/*z*: 205; IR (KBr): $\tilde{\nu}$ = 3037 m, 2894 m, 1660 vs, 1552 vs, 1454 s, 1399 s, 1296 s, 1230 s, 1178 vs, 1071 m, 1004 s, 933 m, 902 s, 835 vs, 749 m, 733 m, 605 vs, 549 vs, 523 s cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 5.79 (s, H5), 2.41–2.35 (q, 2H, H7), 1.89 ppm (s, 3H, H8); ^{13}C NMR ([D$_6$]DMSO): δ = 173.921, 160.962, 158.966, 103.888, 24.922, 18.785 ppm; ^{77}Se NMR ([D$_6$]DMSO): δ = 322 ppm; UV/Vis (CH_2Cl_2): λ (log ε) = 310 nm (4.33), 232 nm (4.53).

*nPrSeU (**3**)*: $C_7H_{10}N_2OSe$; yield: 68%; m.p. 189–190°C; MS: *m*/*z* 219; elemental analysis calcd (%): C 38.72, H 4.64, N 12.90; found: C 38.52, H 4.32, N 12.52; IR (KBr): $\tilde{\nu}$ = 3477 w, 3416 w, 3032 s, 2919 s, 1659 vs, 1623 vs, 1542 vs, 1440 s, 1383 m, 1332 m, 1281 m, 1240 s, 1163 vs, 1009 m, 953 m, 902 w, 815 s, 789 w, 554 s, 523 s cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 10.87–10.79 (d, NH1, NH3), 5.80 (s, H5), 2.49–2.33 (t, 2H, H7), 1.58–1.46 (m, 2H, H8), 0.87–0.83 ppm (t, 3H, H9); ^{1}H NMR ($CDCl_3$): δ = 5.99(s), 2.51–2.45(m), 1.73–1.64(t), 1.03–0.85 (m) ppm; ^{1}H NMR ((CD$_3$)$_2$CO): δ = 5.84 (s, H5), 2.52 (t, 2H, H7), 1.68 (m, 2H, H8), 0.98 ppm (t, 3H, H9); ^{1}H NMR (CD_3OD): δ = 5.88(s), 2.43(m), 1.64(t), 0.98 ppm (m); ^{13}C NMR ([D$_6$]DMSO): δ = 173.722, 160.428, 156.931, 104.563, 33.108, 20.646, 13.254 ppm; ^{13}C NMR ((CD$_3$)$_2$CO): δ = 176.2, 160.9, 157.6, 105.2, 34.6, 21.7, 13.6 ppm; ^{77}Se NMR ([D$_6$]DMSO): δ = 325 ppm; UV/Vis (CH_2Cl_2): ν (log ε) = 312 nm (4.39), 231 nm (4.46).

*iPrSeU (**4**)*: $C_7H_{10}N_2OSe$; yield: 45%; m.p. 219–220°C; elemental analysis calcd (%): C 38.72, H 4.64, N 12.90; found: C 38.18, H 4.59, N 12.03; MS: *m*/*z*: 219; IR (KBr): $\tilde{\nu}$ = 3140 m, 2914 m, 1655 vs, 1614 s, 1547 vs, 1445 w, 1383 s, 1296 m, 1245 m, 1158 vs, 1076 s, 1004 s, 943 w, 902 m, 825 s, 769 m, 635 m, 549 s cm^{-1}; ^{1}H NMR ([D$_6$]DMSO): δ = 5.80 (s, H5), 2.78–2.64 (m, H7), 1.14–1.11 ppm (d, 6H, H8); ^{13}C NMR ([D$_6$]DMSO): δ = 171.649, 158.477, 99.714, 28.069, 18.301 ppm; UV/Vis (CH_2Cl_2): λ (log ε) = 310 nm (3.9), 233 nm (4.47).

Synthesis of complexes (RSeU)I$_2$ (5–8): The appropriate RSeU (1 mmol, 0.187 g of **1**, 0.203 g of **2**, 0.217 g of **3** or **4**) was added to a dichloromethane solution of iodine in a 1:1 molar ratio under nitrogen and in the dark at 0°C. The mixture was stirred for 24 h, and the orange microcrystalline powders formed were filtered off, dried in air, and stored in a freezer. Crystals of [(*n*PrSeU)I$_2$] (**7**) were grown from chloroform solutions. Recrystallization of **6** and **7** from an acetone solution and resulted in the formation of oxidation products of formula **9** and **10**. Selenium was observed to precipitate from the reaction as a black powder. Crystalline 6-*n*-propyluracil (**11**) was obtained by recrystallization of **7** from MeCN/MeOH (1/1), and may have been formed as a result of the presence of traces of water.

*(MeSeU)I$_2$ (**5**)*: L/I$_2$ = 1/1; yield: 72%; m.p. 163–165°C; elemental analysis calcd (%): C 13.56, H 1.37, N 6.33, I 57.31; found: C 13.57, H 1.19, N 6.06, I 54.23; MS: *m*/*z*: 615, 457, 378, 296, 191; IR (KBr): $\tilde{\nu}$ = 3217 s, 3114 s, 3022 s, 2925 s, 2883 s, 1680 vs, 1639 vs, 1557 vs, 1460 m, 1429 m, 1388 s, 1352 s, 1240 m, 1158 s, 1143 s, 1040 m, 948 m, 825 vs, 748 vs, 712 s, 589 vs, 538 s, 502 s cm^{-1}; ^{1}H NMR ((CD$_3$)$_2$CO): δ = 6.39 (s), 5.96 (s), 2.68–2.62 (m), 1.21–1.17 ppm (m); ^{77}Se NMR ((CD$_3$)$_2$CO): δ = 361.7, 361.9 ppm (shoulder); UV/Vis (CH_2Cl_2): λ (log ε) = 498 nm (3.45), 313 nm (4.57), 228 nm (4.32).

*(EtSeU)I$_2$ (**6**)*: L/I$_2$ = 1/1; yield: 53%; m.p. 136–138°C; elemental analysis calcd (%): C 15.77, H 1.76, N 6.13, I 55.55; found: C 15.68, H 1.73, N 5.89, I 55.99; MS: *m*/*z*: 575, 501, 421, 407, 325, 155; IR (KBr): $\tilde{\nu}$ = 1675 vs, 1634 vs, 1547 vs, 1465 m, 1388 m, 1291 m, 1158 m, 1071 w, 922 w, 835 s, 748 s, 692 w, 579 m cm^{-1}; ^{1}H NMR ((CD$_3$)$_2$CO): δ = 6.40 (s), 6.04 (s), 2.82–2.77 (q), 2.70–2.65 (q), 1.42–1.35 ppm (m); ^{77}Se NMR

($(CD_3)_2CO$): δ = 362 ppm; UV/Vis (CH_2Cl_2): λ ($\log\varepsilon$) = 498 nm (3.33), 314 nm (4.49), 227 nm (4.26).

*(nPrSeU)I_2 (**7**)*: L/I_2 = 1/1; yield: 54%; m.p. 190–193°C; elemental analysis calcd (%): C 17.85, H 2.14, N 5.95, I 53.90; found: C 17.19, H 1.84, N 5.40, I 53.70; MS: *m/z*: 931, 807, 593, 457, 434, 353, 340, 298, 169; IR (KBr): $\tilde{\nu}$ = 3554 m, 3473 s, 3411 s, 3237 m, 3191 m, 3114 s, 3017 s, 2930 s, 2858 w, 1685 vs, 1634 vs, 1557 vs, 1475 s, 1393 s, 1332 m, 1271 m, 1230 m, 1153 s, 1096 m, 1015 w, 963 w, 912 m, 830 s, 743 s, 702 m, 610 b, 569 s, 533 m cm^{-1}; ^1H NMR ($CDCl_3$): δ = 5.87 (s), 2.39 (m), 1.67 (t), 1.03 (m) ppm; ^1H NMR ($(CD_3)_2CO$): δ = 6.30 (s), 5.86 (s), 2.72 (m), 2.53 (t), 1.70 (m), 0.98 ppm (m); ^1H NMR (CD_3OD): δ = 6.47 (s), 5.97 (s), 2.45 (m), 1.70 (t), 0.99 ppm (m); ^{77}Se NMR ($(CD_3)_2CO$): δ = 362.4 (low), 358.7 ppm (high); UV/Vis (CH_2Cl_2): λ ($\log\varepsilon$) = 504 nm (2.97), 315 nm (4.28), 228 nm (4.10).

*(iPrSeU)I_2 (**8**)*: L/I_2 = 1/1; yield: 81%; m.p. 148–150°C; elemental analysis calcd (%): C 17.85, H 2.14, N 5.95, I 53.90; found: C 17.46, H 1.79, N 5.87, I 53.04; MS: *m/z*: 571, 477, 434, 353, 340, 169; IR (KBr): $\tilde{\nu}$ = 1685 vs, 1624 vs, 1557 vs, 1465 s, 1399 w, 1306 w, 1224 s, 1194 s, 1173 s, 1066 s, 1015 m, 927 m, 897b, 851 m, 830 m, 687 w, 656 m cm^{-1}; UV/Vis (CH_2Cl_2): λ ($\log\varepsilon$) = 500 nm (3.27), 314 nm (4.36), 228 nm (4.32).

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