Synthesis and Characterization of $(PTU)I_2$ (PTU = 6-*n*-propyl-2-thiouracil) and $(CMBZT)I_2$ (CMBZT = 5-chloro-2-mercaptobenzothiazole) and Possible Implications for the Mechanism of Action of Anti-Thyroid Drugs

Constantinos D. Antoniadis,[a] Ghada J. Corban,[a] Sotiris K. Hadjikakou,*[a] Nick Hadjiliadis,*[a] Maciej Kubicki,[b] Stephanie Warner,[c] and Ian S. Butler[c]

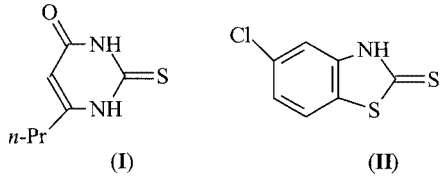
Keywords: Bioinorganic chemistry / Charge transfer / Iodine / S ligands / Nitrogen heterocycles

Direct reaction of 6-*n*-propyl-2-thiouracil (PTU), a widely used anti-thyroid drug against hyperthyroidism (Graves' disease), or 5-chloro-2-mercaptobenzothiazole (CMBZTH) with iodine in a molar ratio of 1:1 resulted in the formation of the charge-transfer (CT) complexes $[(PTU)I_2]$ (**1**) or $[(CMBZT)I_2]$ (**2**). All reactions were carried out in dichloromethane and water solutions. Compounds **1** and **2** were characterized by elemental analyses, FT-Raman, FT-IR, UV/Vis and ^1H NMR spectroscopy. The crystal structures of both complexes were determined by X-ray diffraction at 120(1) K (**1**) and 293(2) K (**2**). The charge-transfer nature of the bonds in the adducts **1** and **2** was verified by the lengthening of the I–I bond lengths as compared to the S–I bond lengths and by the characteristic CT bands observed in the UV spectra of the complexes. Compound **1** $[(C_7H_{10}N_2OS)I_2]$ [monoclinic with space group $P2_1/c$ and a = 9.8501(7), b = 10.3101(7), c = 12.0287(8) Å, β = 99.707(6)°, Z = 4] consists of a propylthiouracil ligand bonded with an iodine atom through sulfur. Extended intermolecular N–H···O contacts link the molecules forming a supramolecular assembly. Compound **2** $\{(C_7H_4ClNS_2)I_2\}$ [orthorhombic, space group $P2_12_12_1$, a = 4.1650(10), b = 9.691(2), c = 28.471(6) Å, Z = 4] consists of a 5-chloro-2-mercaptobenzothiazole ligand bonded with an iodine atom through sulfur. An extended intermolecular linkage via I···H–N bonds leads to the formation of an extended structure. Attempts to draw conclusions on the behavior of a thioamide — when used as an anti-thyroidal drug — towards iodine have been made.

Introduction

The most commonly employed anti-thyroidal drugs for the treatment of hyperthyroidism (Graves' disease) are 6-*n*-propyl-2-thiouracil (PTU), *N*-methylimidazoline-2-thione (methimazole) (MMI) and 3-methyl-2-thioxo-4-imidazoline-1-carboxylate (carbimazole) (CBZ).[1–2] They have been found to inhibit the formation of 3,5,3′-triiodothyronine (T3) and 3,5,3′,5′- tetraiodothyronine (T4) hormones by blocking the metabolism of iodine (Scheme 1).[3] Therefore, there is an increasing interest in the study of charge-transfer (CT) complexes of iodine with thioamides or thiones,[2,4–7] not only for the clarification of the iodine binding mechanism but also for the development of new anti-thyroidal agents.

Although much work has been carried out with these drugs, structural data on their CT complexes with I_2 were only reported very recently for the complex with MMI.[8] Herein we report the structural and spectroscopic characterisation of two new iodine complexes with the heterocyclic thioamides 6-*n*-propyl-2-thiouracil (PTU, I) and 5-chloro-2-mercaptobenzothiazole (CMBZT, II) $[(PTU)I_2]$ (**1**) and $[(CMBZT)I_2]$ (**2**). PTU is used in the treatment of hyperthyroidism while CMBZT was used for comparison purposes.

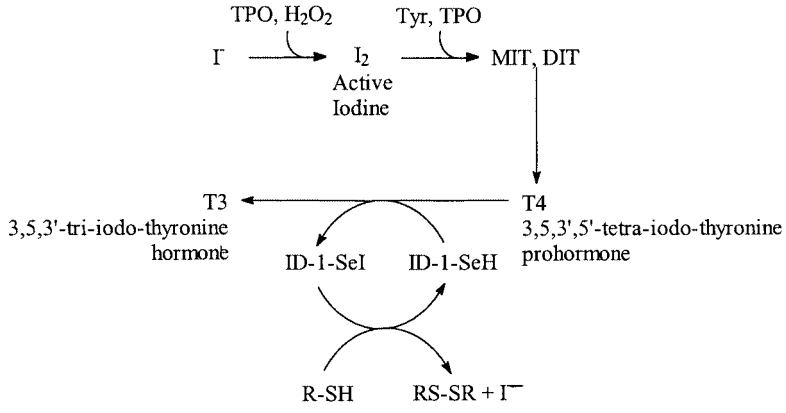


(I) (II)

Results and Discussion

Dark crystals of the complexes, suitable for single crystal analysis by X-ray crystallography, were grown by slow evaporation of the filtrates resulting from the reaction of iodine with the appropriate thioamide in 1:1 or 2:1 molar ratios in

[a] Section of Inorganic and Analytical Chemistry, Department of Chemistry, University of Ioannina, 45110 Ioannina, Greece
Fax: (internat.) +30-26510-44831
E-mail: nhadjil@cc.uoi.gr
[b] Department of Chemistry, A. Mickiewicz, University, ul. Grunwaldzka 6, 60-780 Poznan, Poland
[c] Department of Chemistry, McGill University, 801 Sherbrooke, Montreal Quebec, Canada H2A 2 K6



Scheme 1. Mechanism of TPO-catalyzed iodination reactions (MIT = 3-monoiodotyrosine and DIT = 3,5-diiodotyrosine)

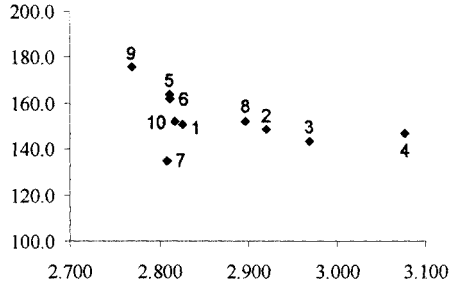


Figure 1. Correlation between ν(I-I) Raman bands of the adducts [{(bztzdtH)I_2}·I_2][7a] (**3**; bztzdtH = benzothiazole-2-thione) ν(I-I)= 143.7 cm^{-1}; [(bztzdtH)I_2][7a] (**4**) ν(I-I) = 147 cm^{-1}, [ptc·I_2][5a] (**5**; ptc = 1,3-dithiacyclohexane-2-thione) ν(I-I)= 164 cm^{-1}; [ttb·I_2][5a] (**6**; ttb = 4,5-ethylenedithio-1,3-dithiole-2-thione) ν(I-I) = 162 cm^{-1}; [mdtt·I_2][5c] [**7**; mdtt = 4,5-bis(methylsulfanyl)-1,3-dithiole-2-thione] ν(I-I) = 136 cm^{-1}; [mbit·I_2][6a] [**8**; mbit = 1,1-methylenebis(3-methyl-4-imidazoline-2-thione)] ν(I-I) = 152 cm^{-1}; [bzoxtH·I_2][6b] (**9**; bzoxtH = benzoxazole-2-thione) ν(I-I) = 176 cm^{-1}; [dmimdtH·I_2][6d] (**10**; dmimdtH = 5,5-dimethylimidazoline-2,4-dithione) ν(I-I) = 152 cm^{-1} and compounds **1** and **2**

dichloromethane. The reactions were also carried out in H_2O. The insoluble dark brown powders obtained were recrystallized from dichloromethane.

The structure of compound **1** shows that the PTU ligand, with anti-thyroidal activity, is able to retain one iodine molecule. The formulae of complexes **1** and **2** were first deduced from elemental analysis and spectroscopic data. Both complexes are highly soluble in organic solvents and their crystals are stable in air, although they were stored in darkness in a refrigerator.

Spectroscopy

Vibrational Spectroscopy

New bands appearing at 153 and 152 cm^{-1} in the far-IR spectra of compounds **1** and **2**, respectively, were assigned to the ν(I−I) stretching vibration modes.[7a] The ν(I−S) bond vibration for the [{(bztzdtH)I_2}·I_2],[7a] [(bztzdtH)I_2][7a] and [{(bzimtH)I_2}$_2$·I_2·H_2O][7a] complexes was observed at 281−280 cm^{-1} and 255−254 cm^{-1}. Here, new bands appear at 250 and 247 cm^{-1} for compounds **1** and **2**, respectively, which can be assigned similarly.

The Raman spectra of complexes **1** and **2**, recorded in the 300−50 cm^{-1} region, show an intense band at 150.9 cm^{-1} for **1** and 148.9, 123.9 cm^{-1} for **2**; these bands are attributed to the ν_1(I−I) vibration of coordinated I_2 moieties.[7a] Iodine gives a band at 180 cm^{-1} ν(I-I) in the solid state.[7a] This shifts to lower frequencies upon coordination to a donor atom because of the reduction of the I−I bond strength. According to Deplano's classification[5a] compound **1** can be classified as being of type **A**, with a weak sulfur-iodine interaction (D···I−I), while compound **2** is of type **B**, with a stronger such interaction (D−I−I). Additionally, complexes **1** and **2** confirm the linear correlation of the d(I−I) bond lengths vs. ν(I-I) FT-Raman frequencies proposed by Deplano et.al.[9] (Figure 1).

UVIVis Spectroscopy

The visible spectra of the thione-iodine adducts in dichloromethane or chloroform exhibit one distinct absorption band at 495−505 nm, assigned to the "blue shift" band of I_2,[6h] which appears at 504 nm in free I_2 in CH_2Cl_2.[6e]

A shoulder in the range 310−360 nm could be assigned to a charge-transfer band from the HOMO of the donor to the iodine LUMO (σ_π*).[2a,5a,5d,6a] It should be noted that the CT (charge transfer) bands are not recognizable for complexes **1** and **2**, as they are most probably covered by the intra-ligand transitions ($\pi^* \leftarrow \pi$ or $\pi^* \leftarrow$ n) occurring at almost the same wavelength. The bands, however, are enhanced in intensity, with increased coefficients, in the complexes. The absorption bands at 285.5 nm in the spectrum of complex **1** and at 336 nm in the case of complex **2** were attributed to intra-ligand ($\pi^* \leftarrow \pi$) transitions.

Thermal Analysis

Thermal analysis in flowing nitrogen shows that complex **2** decomposes in two stages. The TGA and DTA data curves for complex **2** show that the first stage of its decomposition (90−120 °C) is connected with an endothermic effect and involves a 54.7% mass loss consistent with the loss of iodine (calculated mass loss 55.7%). The second stage of its decomposition (180−200 °C) connected

with an endothermic effect and involving a 31.1% mass loss is consistent with the loss of the thione.

Crystal and MolecularStructures of $[(PTU)I_2]$ (1) and $[(CMBZT)I_2]$ (2)

ORTEP diagrams of molecules **1** and **2**, as well as selected bond lengths and angles, are shown in Figure 2 and 3, respectively.

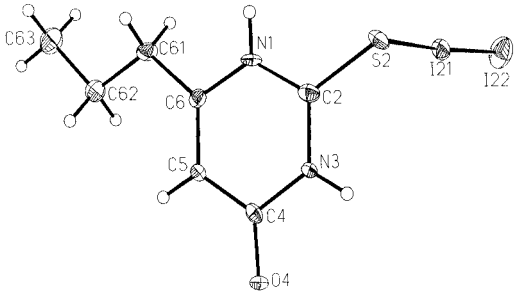


Figure 2. ORTEP diagram of molecule **1** together with the atomic numbering scheme; selected bond lengths (Å), angles [°] and torsion angles [°]: I(21)−I(22) 2.8264(4), S(2)−I(21) 2.7805(10), C(2)−S(2) 1.696(4), C(2)−N(3) 1.358(4), N(1)−C(2) 1.342(5), N(1)−C(6) 1.382(4), N(3)−C(4) 1.396(4) C(4)−O(4) 1.244(4), C(4)−C(5) 1.430(5), C(5)−C(6) 1.362(5); C(2)−S(2)−I(21) 96.05(12), S(2)−I(21)−I(22) 175.85(2), N(3)−C(2)−S(2)−I(21) 85.0(3), N(1)−C(2)−S(2)−I(21) −95.9(3), C(2)−S(2)−I(21)−I(22) −177.0(3)

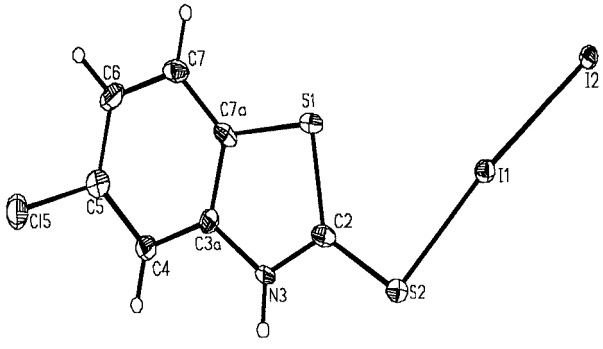


Figure 3. ORTEP diagram of molecule **2** together with the atomic numbering scheme; selected bond lengths (Å), angles [°] and torsion angles [°]: I(1)−I(2) 2.9205(7), I(1)−S(2) 2.634(2), S(2)−C(2) 1.680(6), N(3)−C(2) 1.344(7), S(1)−C(2) 1.746(5), S(1)−C(7A) 1.753(5); S(2)−I(1)−I(2) 173.78(4), C(2)−S(2)−I(1) 105.07(19), I(2)−I(1)−S(2)−C(2) −157.1(4), I(1)−S(2)−C(2)−N(3) 167.9(4), I(1)−S(2)−C(2)−S(1) −13.7(4)

The crystal structures of **1** and **2** consist of a thione ligand bonded to an iodine atom through sulfur, with S−I values of 2.7805(10) Å in **1** (Figure 2), and2.634(2) Å in **2** (Figure 3). The corresponding I−I bond lengths [2.8264(4) Å in **1** and 2.9205(7) Å in **2**] are longer than in iodine itself [gas phase: 2.677 Å;[6e] crystal: 2.715 Å at 110 K[6e]] as a result of the S···I interaction.

Extended intermolecular hydrogen bonding N(1)−H(1)···O(4)#1 [1.96 Å, with N(1)···O(4)#1 = 2.791(4) Å (x, $-y + 1/2$, $z - 1/2$)] and N(3)−H(3)···O(4)#2 [2.02 Å, with N(3)···O(4)#2 = 2.881(4)#2 Å ($-x + 1$, $-y$, $-z + 1$)] is found in complex **1** (Figure 4a). The absence of I···H−N hydrogen bonding in complex (**1**) is due to the perpendicular arrangement of iodine towards the plane of the C=S bond of PTU (vide infra). Since the presence of I···H−N hydrogen bonding in methimazole (MMI) and other related anti-thyroid drugs such as thiazolidine-2-thione (tzdtH) has been shown to play a crucial role in the inhibition[7a,8] this indicates that the inhibition of tyrosil iodination by anti-thyroid drugs should be different in the case of PTU than MMI or thzdtH. In the case of complex **2**, an intermolecular I(2)#2···H(3)−N(3) interaction [2.76 Å, with I(2)#2···N(3) = 3.573(4) Å ($-x + 1$, $y + 1/2$, $-z + 3/2$)] leads to the formation of a supramolecular assembly (Figure 4b).

The X−C=S···I torsion angles for the complexes are N(1)−C(2)−S(2)−I(21) = −95.9(3)° and N(3)−C(2)−S(2)−I(21) = 85.0(3)° for **1**, and I(1)−S(2)−C(2)−S(1) = −13.7(4)° and I(1)−S(2)−C(2)−N(3) = 167.9(4) for **2**. Thus, compound **1** can be considered to contain an almost perpendicular arrangement of iodine atoms with respect to the X−C=S plane. To the best of our knowledge this is the second structurally characterised molecule with such an arrangement, the second being [mbit·I_2].[6a] Examples include {I-S-C-S = −2.3(12)° and I-S-C-N = 174.7(13) in [{(bztzdtH)I_2}·I_2];[7a] I-S-C-S = −15.6(14)° and I-S-C-N = 166.5(15)° in [(bztzdtH)I_2];[7a] I-S-C-N = 3.0(19)° and I-S-C-N′ = −179.7(13)° in [{(bzimtH)I_2}$_2$·I_2·H_2O];[7a] I-S-C-X = −1.5(9)° in [mdtt·I_2];[5c] and I-S-C-X = −96.4(4)° in [mbit·I_2][6a]}. Compound **2**, on the other hand, can be considered as having an almost co-planar arrangement. Finally, the values for the S−I−I angles also imply an almost linear arrangement [S(2)−I(21)−I(22) = 175.85(2)° in (**1**) and S(2)−I(1)−I(2) = 173.78(4)° in (**2**)].

According to the value of the I−I bond order (n) defined by Pauling's equation:[10a]

$$d(\mathrm{I-I}) = d_o - 0.85 \cdot \log(n)$$

where d_o is the I−I bond length of I_2 in the gas phase (2.67 Å),[10b] Bigoli et al.[6a] have classified I_2 adducts into three classes: types **A**, **B** and **C**. When the value of the I−I bond order (n) is greater than or equal to 0.6 [d(I−I) < 2.85 Å] the adduct is classified as type **A**, while if n is less than or equal to 0.4 [d(I−I) > 3.01 Å] the compound is of type **C**;[6a] compounds with intermediate values are of type **B**.[6a] The I−I bond-order values calculated for the complexes studied in this work are 0.654 and 0.507 for complexes **1** and **2**, respectively. Therefore, complex **1** can be classified as type **A**, with a weak S−I interaction, while complex **2** is of type **B**. This is consistent with the classification derived from the spectroscopic data above. Thus, PTU forms a weak CT complex with iodine, in contrast to CMBZT or thiazolidine-2-thione (tzdtH). TzdtH has also been used as anti-thyroidal agent.[1] This molecule reacts with iodine in a molar ratio of 1:2 to form the strong CT

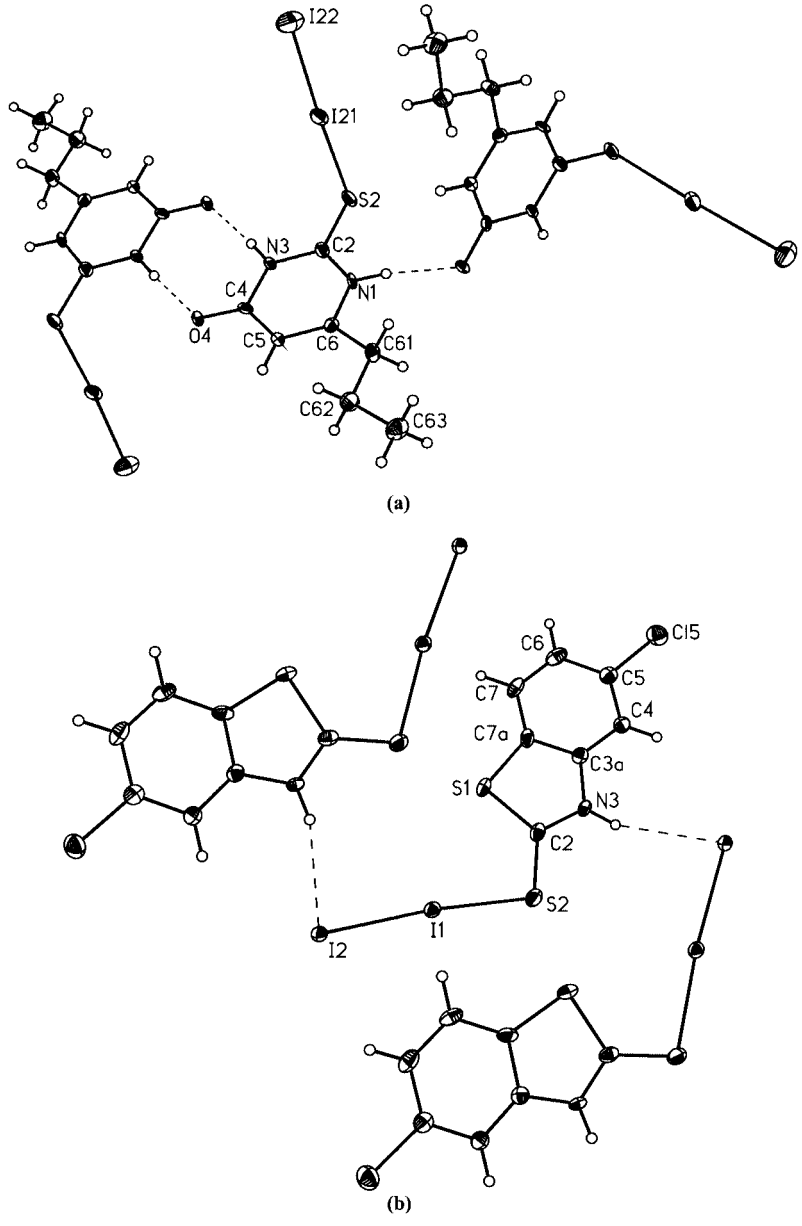


Figure 4. Intramolecular linkages via: (a) N−H···O interactions in **1** and (b) N−H···I interactions in **2**

complex $[\{(tzdtH)_2I^+\}\cdot I_3^-\cdot 2I_2]$,[7a] and is able to retain a total of four iodine molecules per two ligand molecules. On the other hand, MMI reacts with iodine to yield a CT complex which consists of the dication of the disulfite of MMI and I_8^{2-} counteranions $[(C_4H_6N_2S)_2]I_8$.[8] These findings also confirm that the inhibition of tyrosil iodination by anti-thyroid drugs should be different in the case of PTU than MMI or tzdtH, as proposed by Nakataka et.al.[11]

Conclusions

In conclusion, thioamides exhibiting anti-thyroidal activity against hyperthyroidism (Graves' disease) can be classified into two categories: (i) thioamides, such as MMI[8] or tzdtH,[7a] which are strong donors to iodine and form ionic salts, and (ii) thioamides like PTU, which are able to form weak charge-transfer molecules with iodine. Thioamides with intermediate donor activity to iodine — CMBZT, benzothiazole-2-thione (bztdtH)[7a] or benzimidazole-2-thione (bzimtH)[7a] — are able to bind only one I_2 molecule strongly and show no anti-thyroid activity. Thus, it seems that whereas drugs like MMI etc. interfere with the iodination mechanism by forming active iodine species in competition with the tyrosil residues of thyroglobuline[8,12,13] (Scheme 1), drugs like PTU appear to interfere either in the formation of the thyroid peroxide (TPO)-iodonium complex[12,13] or inhibit the activity of iodothyronine deiodinase (ID-1-SeH), an enzyme responsible for the monodeiodination of the **T4** prohormone to the **T3** hormone, as proposed by Berry et al.[13a] and later supported by du Mont et al.[13b] (Scheme 1). This is in agreement with

the proposal of Nakataka et al.,[11] supporting the difference in the inhibition mechanism of these type of drugs.

Experimental Section

Synthesis and Crystallisation of the Molecules: Complexes **1** and **2** were prepared by mixing dichloromethane solutions of iodine with a suspension of the appropriate thione in dichloromethane solution in molar ratios of 1:1 or 2:1, in air, at 0 °C, with continuous stirring, for 24 hours. The mixtures were then filtered and the resulting clear solutions were kept in the refrigerator for several days. Dark crystals of the complexes suitable for single-crystal analysis by X-ray crystallography were then grown and isolated by filtration. The reactions were also carried out in H_2O. The insoluble dark brown powders obtained were recrystallized from dichloromethane to yield the same products as previously.

Complex 1: Yield 0.085 g, (20%); m.p. 144−146 °C. $C_7H_{10}N_2I_2OS$ (424.0): calcd. C 19.83, H 2.37, N 6.61, S 7.56; found C 20.29, H 2.43, N 6.68, S 7.79. UV/Vis (CH_2Cl_2): λ_{max} (logε) = 512.5 nm (3.12), 287.5 (4.25). ^{1}H NMR ($CDCl_3$): δ = 10.05 [s, 1 H, HN(3)−C(2)], 9.74 [s, 1 H, HN(1)−C(2)], 2.41−2.35 [t, 2 H, $H_2C(61)$-C(6) of *n*-Pr], 1.73−1.26 [m, 2 H, $H_2C(62)$-C(61) of *n*-Pr], 1.06−1.00 [t, 3 H, $H_3C(63)$-C(62) of *n*-Pr] ppm.

Complex 2: Yield 0.050 g, (22%); m.p. 160−165 °C. $C_7H_4ClI_2NS_2$ (455.5): calcd. C 18.46, H 0.88, N 3.08, S 14.08; found C 17.90, H 0.63, N 2.80, S 14.07. UV/Vis (CH_2Cl_2): λ_{max} (logε) = 504 nm (2.93), 336 (4.36), 229 (4.41). ^{1}H NMR ($CDCl_3$): δ = 8.02 (s, 2 H, NH), 7.41−7.31 (m, 4 H, aromatic) ppm.

Crystal Data: Data were collected by the ω-scan technique in the $\theta-2\theta$ range 3.53 to 29.30° for **1** and 3.55 to 29.24° for **2** on a KUMA KM4CCD four-circle diffractometer[14a] with CCD detector, using graphite-monochromated Mo-K_α (λ = 0.71073 Å). Cell parameters were determined by a least-squares fit.[14b] All data were corrected for Lorentz-polarization effects and absorption.[14b] The structures were solved by direct methods with SHELXS-97[15] and refined by full-matrix least-squares procedures on F^2. All non-hydrogen atoms were refined anisotropically, hydrogen atoms were located at calculated positions and refined as a "riding model" with isotropic thermal parameters fixed at 1.2-times the U_{eq}'s of the appropriate carrier atom.

1: $C_7H_{10}I_2N_2OS$, mol. wt. = 424.03, monoclinic space group $P2_1/c$, a = 9.8501(7), b = 10.3101(7), c = 12.0287(8) Å, β = 99.707(6)°, V = 1204.09(14) Å^3, Z = 4, T = 120(1) K, ρ(calcd.) = 2.339 g cm^{-3}, μ = 5.365 mm^{-1}, reflections collected 2997. Final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0323, $wR2$ = 0.0745.

2: $C_7H_4ClI_2NS_2$, mol. wt. = 455.48, orthorhombic space group $P2_12_12_1$, a = 4.1650(10), b = 9.691(2), c = 28.471(6) Å, V = 1149.2(4) Å^3, Z = 4, T = 293(2) K, ρ(calcd.) = 2.633 g cm^{-3}, μ = 6.023 mm^{-1}, reflections collected 7301. Final R indices [$I > 2\sigma(I)$]: $R1$ = 0.0275, $wR2$ = 0.0528.

CCDC-189659 (**1**) and -189660 (**2**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) +44-1223/336-033; E-mail: deposit@ccdc.cam.ac.uk].

Acknowledgments

This work was carried out in partial fulfillment of the requirements for an MSc thesis of C. D. A. (**1**) and G. J. C. (**2**) within the graduate program EPEAEK in Bioinorganic Chemistry financed by the Ministry of Education of Greece and coordinated by Professor N. Hadjiliadis. A NATO grant awarded to N. H. and I. S. B. is also acknowledged.

[1] [1a] Martidale, *The Extra Pharmacopoeia*, 28th edition, The Pharmaceutical Press, London **1982**. [1b] J. Buxeraud, *Traite de Chimie therapeutique*, Tec et Doc Lavoisier, Paris, **1995**, vol 4, ch 18.

[2] [2a] C. Laurence, M. J. El Ghomari, J-Y. Le Questel, M. Berthelot, R. Mokhlisse, *J. Chem. Soc., Perkin Trans.* **1998**, *2*, 1545−1551. [2b] C. Laurence, M. J. El Ghomari, M. Lucon, *J. Chem. Soc., Perkin Trans.* **1998**, *2*, 1159−1162. [2c] C. Laurence, M. J. El Ghomari, M. Berthelot, *J. Chem. Soc., Perkin Trans.* **1998**, *2*, 1163−1166.

[3] [3a] J. Leclerc, J. Orgiazzi, B. Rousser, J. L. Schlienger, J. L. Wemeau, *La Thyroide*, Exapnsion Scientifique Francaise, Paris **1992**. [3b]C. Raby, J. Buxeraud, *Eur. J. Med Chem.* **1980**, *15*, 425−430. [3c] J. Buxeraud, A. B. Absil, J. Claude, C. Raby, G. Catazano, C. Beck, F. Claude, *Eur. J. Med Chem.* **1985**, *20*, 43−50.

[4] [4a] M. Esseffar, W. Bouab, A. Lamsabhi, J. L. M. Abboud, R. Notario, M. Yanez, *J. Am. Chem. Soc.* **2000**, *122*, 2300−2308. [4b] P. D. Boyle, J. Christie, T. Dyer, S. M. Godfrey, I. R. Howson, C. McArthur, B. Omar, R. G. Pritchard, G. R. Williams, *J. Chem. Soc., Dalton Trans.* **2000**, 3106−3112.

[5] [5a] F. Bigoli, P. Deplano, A. Ienco, C. Mealli, M. L. Mercuri, M. A. Pellinghelli, G. Pintus, G. Saba, E. F. Trogu, *Inorg. Chem.* **1999**, *38*, 4626−4636. [5b] F. Demartin, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis, G. Verani, *Polyhedron* **1999**, *18*, 3107−3113. [5c] N. Bricklebank, P. J. Skabara, D. E. Hibbs, M. B. Hursthouse, K. M. A. Malik, *J. Chem. Soc., Dalton Trans.* **1999**, 3007−3014. [5d] M. C. Aragoni, M. Arca, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis, G. Verani, *Coord. Chem. Rev.* **1999**, *184*, 271−290.

[6] [6a] F. Bigoli, P. Deplano, M. L. Mercuri, M. A. Pellinghelli, A. Sabatini, E. F. Trogu, A. Vacca, *J. Chem. Soc., Dalton Trans.* **1996**, 3583−3589. [6b] F. Cristiani, F. A. Devillanova, F. Isaia, V. Lippolls, G. Verani, F. Demartin, *Polyhedron* **1995**, *14*, 2937−2943. [6c] F. Demartin, P. Deplano, F. A. Devillanova, F. Isaia, V. Lippolis, G. Verani, *Inorg. Chem.* **1993**, *32*, 3694−3699. [6d] F. Cristiani, F. Demartin, F. A. Devillanova, F. Isaia, G. Saba, G. Verani, *J. Chem. Soc., Dalton Trans.* **1992**, 3553−3560. [6e] F. Freeman, J. W. Zi1ler, H. N. Po, M. C. Keindl, *J. Am. Chem. Soc.* **1988**, *110*, 2586−2591. [6f] F. H. Herbstein, W. Schwotzer, *J. Am. Chem. Soc.* **1984**, *106*, 2367−2373. [6g] F. H. Herbstein, W. Schwotzer, *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 219. [6h] F. A. Devillanova, G. Verani, *Tetrahedron* **1979**, *35*, 511−514.

[7] [7a] V. Daga, S. K. Hadjikakou, N. Hadjiliadis, M. Kubicki, J. H. Z. dos Santos, I. S. Butler, *Eur. J. Inorg. Chem.* **2002**, 1718−1728. [7b] J. H. Z. dos Santos, I. S. Butler, V. Daga, S. K. Hadjikakou, N. Hadjiliadis, *Spectrochimica Acta Part A* **2002**, *58*, 2725−2735.

[8] M. C. Aragoni, M. Arca, F. Demartin, F. A. Devillanova, A. Garau, F. Isaia, V. Lippolis, G. Verani, *J. Am. Chem. Soc.* **2002**, *124*, 4538−4539.

[9] P. Deplano, F. A. Devillanova, J. R. Ferraro, F. Isaia, V. Lippolis, M. L. Mercuri, *Appl. Spectrosc.* **1992**, *46*, 1625−1629.

[10] [10a] L. Pauling, *The Nature of the Chemical Bond*, 3rd edn, Cornell University Press, Ithaca, New York, **1960**. [10b] H. B. Burgi, *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 460−473.

[11] A. Nakataka, H. Hidaka, *J. Clin. Endocrinol. Metab.* **1976**, *43*, 152−158.

[12] [12a] D. R. Morris, L. P Hager, *J. Biol. Chem.* **1966**, *241*, 3582−3589. [12b] A. Taurog, *Endocrinology* (Ed.: L. DeGroot), Academic Press, Inc. London, **1979**, vol 1, 331.

[13] [13a] M. J. Berry, J. D. Kieffer, J. W. Harney, P. R. Larsen, *J. Biol. Chem.* **1991**, *266*, 14155−14158. [13b] W. W. du Mont, G.

Mugesh, C. Wismach, P. G. Jones, *Angew. Chem. Int. Ed.* **2001**, *40*, 2486−2489.
[14] [14a] KUMA KM-4CCD user manual, KUMA Diffraction, Wroclaw, Poland 1999. [14b] CrysAlis, for reduction of the data from KUMA CCD diffractometer, KUMA Diffraction, Wroclaw, Poland 1999.
[15] G. M. Sheldrick, SHELXS-97 (Release 97-2), for crystal structure solution, and SHELXL-93, for refinement of crystal structures, Institut fur Anorganische Chemie, University of Göttingen, Germany.

Received November 12, 2002
[I02621]