Structure of a Potent Antithyroid Drug, 6-Propyl-2-thiouracil

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Synopsis. The crystal strure of 6-propyl-2-thiouracil (PTU), an antithyroid drug, has been determined as a 2:1 complex with 1,4-dioxane [$(C_7H_{10}N_2OS)_2(C_4H_8O_2)$]. The crystals are monoclinic, space group $P2_1/a$, with $a=8.983(5)$, $b=23.706(12)$, $c=4.942(2)$ Å, $\beta=95.79(3)°$, $V=1047.1(9)$ Å^3, $Z=4$, $D_x=1.36$ Mg m^{-3}, $D_m=1.35$ Mg m^{-3}, MW=214.29, λ(Cu $K\alpha$)=1.5418 Å. Final $R=0.098$ for 1575 reflexions.

6-Propyl-2-thiouracil (PTU) is a potent antithyroid drug as well as 2-thiouracil (TU) and 6-methyl-2-thiouracil (MTU). These compounds inhibit the biosynthesis of thyroid hormones and have been used for the treatment of hypothyroidism.[1-3] PTU is also known as a strong inhibitor of monoiodination of thyroid hormones in some tissues, such as liver, kidney or brain.[4,5] Although it appears that PTU inhibits the thyroid peroxidase in the thyroid gland or the deiodinase in some tissues, little is known about the actual mechanisms of these inhibitory effects. In this study, the molecular conformation of PTU is determined by X-ray analysis as a first step for elucidation of these inhibitory mechanisms.

Experimental

PTU and 1,4-dioxane were purchased from Nakarai Chemicals Ltd. Kyoto, Japan. PTU was crystallized from 2%(v/v) 1,4-dioxane aqueous solution by slow evaporation of the solvent at room temperature, and it was found that PTU crystallized as a 2:1 complex with 1,4-dioxane. A brittle needle crystal with the dimensions $0.30\times0.30\times0.15$ mm^3 was sealed in a capillary with mother liquor for X-ray analysis. Intensity data were collected on a Rigaku four-circle diffractometer AFC-5 with graphite-monochromated Cu $K\alpha$ radiation (45 kV, 25 mA) yielding 1809 independent reflexions with $2\theta\leq125°$. The intensities were corrected for Lorenz and polarization factors, but not for absorption. The structure was solved by MULTAN.[6] The positions of 14 non-hydrogen atoms were correctly determined and 14H atoms were located from a difference Fourier map. Refinement was performed by a block-diagonal least squares method up to $R=0.098$. The atomic scattering factors for C, N, O, and S were taken from International Tables for X-Ray Crystallography.[7]

Results and Discussion

The molecular shape of PTU complex with dioxane (2:1) is illustrated in Fig. 1. The final atomic parameters are listed in Table 1. The bond lengths and angles of PTU and dioxane are summarized in Table 2. These values are in good agreement with those of uracil[8] and its related derivatives, 2-thiouracil,[9] 1-methyluracil,[10] 1-ethyl-5-bromouracil,[11] and the dioxane complexes with oxalyl dichloride and oxalyl dibromide,[12] with iodoform[13] and with 1,7-diacetoxy-2,4,6-trinitro-2,4,6-triazaheptane,[14] except C(2)–S bond length of PTU, 1.647(5) Å, which is somewhat shorter than that of TU, 1.67 Å.[9] The propyl group attached to C(6) position forms an extended planar trans conformation. The uracil plane is nearly coplanar with the propyl one and the dihedral angle between the planes is 10.4(5)°. Bond lengths of the propyl group, C(6)–C(7), 1.500(8) Å, C(7)–C(8), 1.516 (8) Å, and C(8)–C(9), 1.532(8) Å are a little shorter in this order than that of the ideal C–C single bond

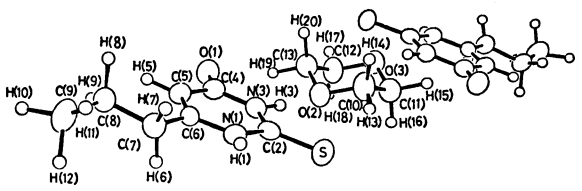

Fig. 1. A view of PTU complex with dioxane and the atomic numbering.

Table 1. Final atomic parameters (positional $\times10^4$, for H $\times10^3$) with e.s.d.'s in parentheses and equivalent isotropic temperature factors (isotropic H)

$$B_{eq}=\frac{4}{3}\Sigma_i\Sigma_j\beta_{ij}a_ia_j.$$

Atom	x	y	z	$B_{eq}(B_{iso})$/Å^2
S	2654(2)	6413(1)	3654(3)	3.89(4)
O(1)	6342(4)	6934(1)	11236(7)	4.39(20)
O(2)	5012(4)	5536(1)	8839(6)	4.15(21)
N(1)	3384(5)	7451(2)	5262(7)	3.01(20)
N(3)	4594(5)	6741(2)	7684(8)	3.24(20)
C(2)	3581(6)	6887(2)	5596(9)	2.83(23)
C(4)	5396(6)	7126(2)	9410(9)	3.21(24)
C(5)	5120(6)	7705(2)	8932(9)	3.13(24)
C(6)	4126(5)	7855(2)	6866(9)	2.73(23)
C(7)	3718(6)	8450(2)	6066(9)	3.78(26)
C(8)	4412(6)	8893(2)	8014(10)	3.87(26)
C(9)	4062(7)	9485(2)	6883(10)	5.64(32)
C(10)	3714(6)	5195(2)	8455(10)	4.55(28)
C(13)	5828(6)	5413(2)	11436(10)	4.30(27)
H(1)	260(5)	761(2)	424(7)	2.6 (1.2)
H(3)	470(5)	632(2)	792(9)	4.9 (1.5)
H(5)	568(5)	802(2)	1020(8)	4.6 (1.4)
H(6)	383(5)	846(2)	415(8)	4.4 (1.4)
H(7)	240(5)	857(2)	609(8)	4.6 (1.3)
H(8)	551(5)	884(1)	887(8)	2.4 (1.2)
H(9)	409(4)	884(1)	1013(8)	2.5 (1.2)
H(10)	300(5)	941(2)	657(9)	5.1 (1.5)
H(11)	407(6)	961(2)	444(10)	9.5 (2.0)
H(12)	495(5)	983(2)	792(7)	4.3 (1.4)
H(13)	276(5)	535(2)	949(8)	4.5 (1.4)
H(14)	316(5)	537(2)	662(7)	2.3 (1.2)
H(19)	700(5)	567(2)	1181(8)	3.4 (1.3)
H(20)	514(6)	558(2)	1312(8)	5.4 (1.5)

Table 2. Intermolecular bond length and bond angles with e.s.d.'s in parentheses

Bond length	l/Å	Bond length	l/Å
S-C (2)	1.647(5)	C (7)-C (8)	1.516(8)
N (1)-C (2)	1.357(6)	C (8)-C (9)	1.532(8)
C (2)-C (3)	1.351(6)	O (2)-C (10)	1.416(6)
N (3)-C (4)	1.398(7)	O (2)-C (13)	1.442(7)
C (4)-C (5)	1.412(7)	C (10)-C (11)	1.499(8)
O (1)-C (4)	1.260(6)	O (3)-C (11)	1.442(7)
C (5)-C (6)	1.335(7)	O (3)-C (12)	1.416(6)
C (6)-C (7)	1.500(8)	C (12)-C (13)	1.499(8)
N (1)-C (6)	1.373(6)		
Bond angle	ϕ/°	Bond angle	ϕ/°
S-C (2)-N (1)	123.3(4)	N(1)-C(6)-C(7)	114.3(4)
S-C (2)-N (3)	122.2(4)	C(6)-C(7)-C(8)	114.2(4)
N(1)-C(2)-N(3)	114.5(4)	C(7)-C(8)-C(9)	110.3(5)
C(2)-N(3)-C(4)	124.4(5)	C(10)-O(2)-C(13)	109.9(4)
O(1)-C(4)-N(3)	118.0(4)	C(11)-O(3)-C(12)	109.9(4)
O(1)-C(4)-C(5)	124.4(5)	O(2)-C(10)-C(11)	109.0(4)
N(3)-C(4)-C(5)	117.5(5)	C(10)-C(11)-O(3)	109.8(4)
C(4)-C(5)-C(6)	118.7(5)	O(3)-C(12)-C(13)	109.0(4)
C(5)-C(6)-N(1)	120.3(5)	C(12)-C(13)-O(2)	109.8(4)
C(5)-C(6)-C(7)	125.3(5)		

known as 1.54 Å. The shortening of the C–C bonds occurs markedly close to the pyrimidine ring. This suggests the resonance effect between the pyrimidine ring and the propyl group, which may explain the extended planar conformation of the propyl group. No disordering of the propyl group was observed. This indicates that the observed trans conformation of the propyl group might be a most stable one in the crystal. The dioxane molecule takes a chair conformation which has been found in the crystals as a stable form.[12–14] The molecular packing of PTU and dioxane in the crystal is shown in Fig. 2. Two PTU and one dioxane molecules are joined together in pairs by the hydrogen bond formation, N(3)–H(3)···O(2) (or O(3)), 2.929(6) Å. A PTU molecule is also connected with adjacent molecules to form endless chains by the hydrogen bond, N(1)–H(1)···O(1), 2.952(5) Å. The sulfur atom at C(2) position does not participate in the hydrogen bond network, while in the crystals structure of TU, the N–H···S hydrogen bond with the length of 3.32 Å was formed.[9] This may explain the reason why the bond length, C(2)–S of PTU is a little shorter than that of TU. No stacking interaction between uracil bases was observed.

The relative antithyroid activity of PTU is 75 and that of MTU is 100 assuming TU as 100.[1] Supposing that the extended planar trans conformation of PTU found in the crystal is dominant as the antithyroid active form, lower antithyroid activity of PTU as compared with MTU or TU may be interpreted by the conformational feature of PTU. The planarity of PTU with the extended planar propyl group may have some negative effects for binding ability of it at the active center of the enzyme by steric hindrance. When thyroid hormones bind to carrier proteins, the 4′-OH group of these participates in a hydrogen bond

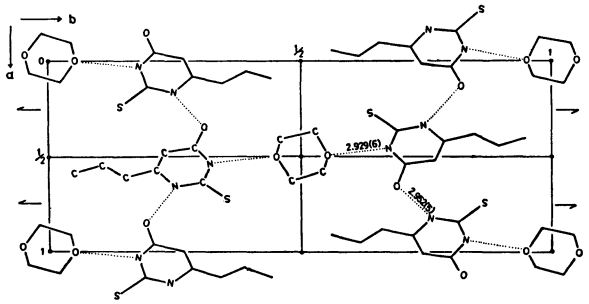

Fig. 2. Packing of the molecules viewed down c. The H atoms are excluded for clarity. The dotted lines represent the hydrogen bonds. Distances are in Å.

formation.[15] The hydrogen bond between PTU and dioxane may be concerned with the role of the 4′-OH group of the thyroid hormones at the active center of the enzyme. The three hydrogen bonds found in this crystal may be indispensable for fixing PTU on the binding site of the enzyme and for the following inhibitory action against the function of peroxidase or deiodinase resulted in the sulfur atom at C(2) position. Unfortunately, no physicochemical data on the interaction between PTU and relative enzymes is available. For this result, systematic studies concerning the effects of PTU on the endocrinal homeostasis may also be desirable.

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