This work was supported by the Donors of the Petroleum Research Fund, administered by the American Chemical Society, and by the University Research Council of Vanderbilt University. Funds for the X-ray diffraction facility were provided through NSF Grant CHE-8908065.

Lists of structure factors, anisotropic displacement parameters and H-atom coordinates have been deposited with the IUCr (Reference: AS1115). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1995). C**51**, 315–318

Thiamin Thiothiazolone Acetone Solvate, $C_{12}H_{16}N_4OS_2.0.5C_3H_6O$

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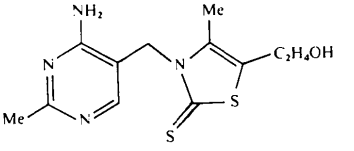
(*Received* 29 *September* 1993; *accepted* 7 *April* 1994)

Abstract

The structure of thiamin thiothiazolone {TTT; 3-[(4-amino-2-methyl-5-pyrimidinyl)methyl]-5-(2-hydroxyethyl)-4-methyl-2(3*H*)-thiazolethione}, originally known as a transition-state analogue of thiamin, is quite different from that of its congener thiamin thiazolone (TT). TTT assumes the *S* conformation [$\varphi_T = \pm 83\ (1)°$; $\varphi_P = \mp 176\ (1)°$], while TT assumes the *V* conformation [$\varphi_T = \pm 104\ (1)°$; $\varphi_P = \mp 74\ (1)°$] with an intramolecular N—H···O hydrogen bond. The conformations of the hydroxyethyl side chains are also different, so that TTT has a close $^{\delta+}S\cdots O^{\delta-}$ electrostatic interaction while TT does not. Crystal packing consists of a three-dimensional hydrogen-bonding network formed by three unique hydrogen bonds. There are two kinds of hydrogen-bonded molecular dimer. The acetone molecule is statistically disordered in the cavity formed by the two centrosymmetrically related pyrimidine base pairs.

Comment

The diphosphate esters of thiamin thiothiazolone (TTT) and thiamin thiazolone (TT) were originally proposed to be transition-state analogues for thiamin diphosphate-dependent enzymic reactions owing to their structural resemblance to the enamine, a reactive intermediate in thiamin catalysis, together with a very high binding affinity (Gutowski & Lienhard, 1976). However, it was suggested later that they are intermediate analogues rather than transition-state analogues and that the lower polarity of these compounds may be the major factor governing their high affinity for the hydrophobic binding site of the apoenzyme (Kluger, Gish & Kauffman, 1984; Kuo & Jordan, 1983). Whether TT and TTT are the transition-state or intermediate analogues or not, these compounds are interesting from a structural viewpoint. In the crystalline state, TT assumes a *V* conformation with an intramolecular N—H···O hydrogen bond (Shin & Kim, 1986). This remains the only crystal structure that remotely resembles Schellenberger's *active V* model of thiamin (Schellenberger, 1967), which has been confirmed from the recently determined crystal structures of transketolase (Lindqvist, Schneider, Ermler & Sundström, 1992), pyruvate oxidase (Muller & Schulz, 1993) and pyruvate decarboxylase (Dyda *et al.*, 1993). Although it is tempting to predict that TTT assumes the same *V* conformation as congeneric TT since the N—H···S hydrogen bond can easily be formed, the X-ray structure of TTT reveals a quite different conformation.



TTT

An *ORTEP*II (Johnson, 1976) drawing of the TTT molecule with the atomic numbering scheme is presented in Fig. 1. The bond distances of the Δ^4-thiazoline-2-thione ring moiety are in excellent agreement (within 1σ) with those of compounds containing the same ring system (Rochester, Berg, Pierrot & Sandström, 1987). The thioketo bond distance of 1.656 (4) Å is also in agreement with those found in thio derivatives of nucleic acid components (Saenger & Suck, 1971). The

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bond distances of thiamin, TT and TTT show systematic variations, such that the S(1)—C(2) and C(2)—N(3) bonds in the thiazoline rings of TTT and TT become longer and the C(4)—C(5) bond becomes shorter than those of thiamin. In thiamin, S(1)—C(2) [*ca* 1.67 (1) Å] is always shorter by *ca* 0.05 Å than S(1)—C(5) [*ca* 1.72 (1) Å], suggesting that the S(1)—C(2) bond of thiamin has more double-bond character than the S(1)—C(5) bond (Kraut & Reed, 1962). However, in TTT, the S(1)—C(2) bond is considerably longer [0.06 (1) Å] than that of thiamin and the S(1)—C(2) and S(1)—C(5) bonds become similar [1.729 (4) and 1.724 (5) Å, respectively]. The same trends hold for TT, but the S(1)—C(2) [1.764 (5) Å] and S(1)—C(5) [1.752 (5) Å] bonds are longer by 0.035 (9σ) and 0.027 (6σ) Å, respectively, than those of TTT. The C(2)—N(3), N(3)—C(4) and C(4)—C(5) bond distances are 1.360 (6), 1.398 (5) and 1.337 (6) Å in TTT and 1.348 (6), 1.420 (6) and 1.331 (7) Å in TT, while their average values are 1.32 (1), 1.39 (4) and 1.36 (1) Å in thiamin, respectively (Cramer, Maynard & Ibers, 1981). The differences in bond distances suggest that the π electrons in the thiazoline ring are less drawn towards the C(2) exocyclic bond in TTT than in TT. These differences are also consistent with the fact the C=S bond has less π-bond energy than the C=O bond (Schmidt, Truong & Gordon, 1987). Despite the significant differences in the thiazoline moieties, the molecular dimensions of the uncharged pyrimidine ring moiety in TTT agree well (within 2σ) with those in TT as well as those of unprotonated thiamin. This is consistent with our early notion that there are no long-range structural interactions between the two ring systems in thiamin analogues (Shin & Kim, 1986).

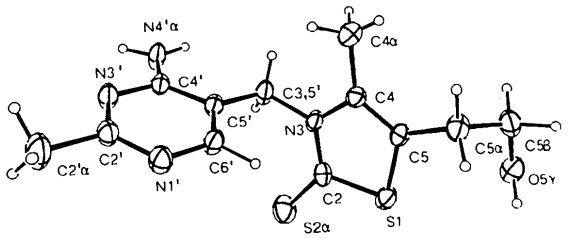

Fig. 1. *ORTEP*II (Johnson, 1976) view of the thiamin thiothiazolone molecule with the atomic numbering scheme.

The largest differences between the bond angles of TT and TTT occur in the N(3)—C(3,5')—C(5') and C(5α)—C(5β)—O(5γ) angles, which are 3.0 (4)° smaller and 3.5 (4)° larger in TTT, respectively. These variations in bond angles are related to differences in the overall molecular conformation and in the conformation of the hydroxyethyl side chain (Shin, Oh, Chae & Yoon, 1993). Other bond angles agree within 4σ. We noted previously that the S(1)—C(2)—N(3) angle of TT is smaller by 3.1 (3)° than that of thiamin, presumably due to the 'fatter' C(2)=O(2α) double bond (Shin & Kim, 1986). This angle is further decreased by 1.3 (3)° in TTT. The thiazoline and pyrimidine rings of TTT are planar with maximum deviations of 0.014 (5) and 0.013 (5) Å and the methylene bridge C(3,5') deviates by 0.083 (5) and 0.022 (5) Å from the two ring planes, respectively. The dihedral angle between the two rings is 86.0 (1)°. The deviation of N(3) from the plane formed by C(2), C(4) and C(3,5') is 0.043 (3) Å and the sum of valence angles around N(3) is 359.8 (6)°.

The conformation of the thiamin-related compounds is characterized by the torsion angles φ_T[C(5')—C(3,5')—N(3)—C(2)] and φ_P[N(3)—C(3,5')—(5')—C(4')] (Pletcher, Sax, Blank & Wood, 1977). TTT assumes the *S* conformation with $\varphi_T = \pm 83.0\ (5)°$ and $\varphi_P = \mp 176.1\ (6)°$, which is characteristic for thiamin analogues with a bulky substituent at C(2). It is quite tempting to speculate that TTT might easily assume a *V* conformation similar to that of TT with an intramolecular N—H···S hydrogen bond comparable with the N—H···O hydrogen bond in TT, since the functional properties of both compounds remain the same. However, replacement of O with S at the C(2) position results in a major change in the molecular conformation. We suggested previously that the conformations of thiamin and its analogues are sensitive to short-range intramolecular contacts, especially between the substituents at C(2) and C(4') and between those at C(4) and C(6') (Shin & Kim, 1986). Crystallization of TTT in the *S* form adds substantial evidence for this notion. In many thiamin structures, S(1) makes a close contact with either O(5γ) or halogen ions due to the partial positive charge on S(1) (Sax, Pulsinelli & Pletcher, 1974). The shortest $^{\delta+}$S···O(5γ)$^{\delta-}$ distance observed thus far is 2.749 Å in DL-2-(α-hydroxybenzyl)oxythiamin.-Cl.HCl.3H_2O (Shin, Pletcher & Sax, 1979). In TTT, S(1) is also close to O(5γ), at a distance of 3.083 (3) Å, which is 0.17 Å shorter than the sum of the van der Waals radii (3.25 Å). In TT, S(1) is quite distant from O(5γ) with a separation of 3.805 (5) Å. The conformation of the hydroxyethyl side chain [$\varphi_{5\alpha}$ = S(1)—C(5)—C(5α)—C(5β) = ± 71.5 (4)° and $\varphi_{5\beta}$ = C(5)—C(5α)—C(5β)—O(5γ) = ∓54.5 (4)°] is similar to that found in thiamin compounds with a close S···O interaction.

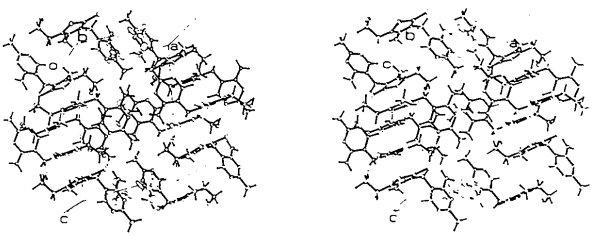

Fig. 2. Stereoscopic *ORTEP*II (Johnson, 1976) packing diagram. The dotted lines denote the hydrogen bonds. Only one of the disordered acetone molecules is shown for clarity.

The crystal-packing interactions (Fig. 2) comprise three unique hydrogen bonds (Table 3). There are two kinds of molecular dimers formed by the hydrogen bonds. Two molecules related by a centre of symmetry at (000) are dimerized *via* O(5γ)—H···N(1′) hydrogen bonds. The N(4′α)—H···N(3′) hydrogen bonds dimerize two molecules related by a centre of symmetry at ($\frac{1}{2}0\frac{1}{2}$), providing quite a large planar region. The two planar base pairs related by a centre of symmetry at ($\frac{1}{2}\frac{1}{2}\frac{1}{2}$) form a large cavity inside the crystal lattice. The large cavity is occupied by an acetone molecule which is statistically disordered around the centre of symmetry at ($\frac{1}{2}\frac{1}{2}\frac{1}{2}$) with a half site occupancy factor. Each acetone molecule is approximately parallel to the planes of the pyrimidine base pairs [dihedral angle 14.8 (9)°] with a mean separation of 3.7 (2) Å. The N(4′α)—H···O(5γ) hydrogen bonds interconnect the molecular dimers to form a three-dimensional hydrogen-bonding network. All these hydrogen-bonding schemes are frequently found in thiamin crystal structures (Shin & Lah, 1987). There are no unusually close contacts shorter than the van der Waals interactions.

Conformational analysis employing molecular-mechanics calculations indicates that the conformational potential-energy surfaces of TT and TTT are quite different in the low-energy region, although the general shapes of the energy maps are similar (Shin, Oh, Chae & Yoon, 1993). TT has a distinct global minimum which corresponds to the *V* form with an N—H···O hydrogen bond, while TTT has two wide minima (*S* and *V*) which have nearly equal energies and similar conformational spaces. This study revealed that the intramolecular N—H···S hydrogen bond in TTT cannot be formed with acceptable hydrogen-bonding geometry, especially in the H···S=C(2) acceptor angle, due to the long C=S bond and the large van der Waals radius of the S atom.

Experimental

The title compound was synthesized according to the method described by Cooks & Sykes (1968) and recrystallized from aqueous acetone solution. The density D_m was measured by flotation.

Crystal data

$C_{12}H_{16}N_4OS_2.0.5C_3H_6O$
M_r = 325.46
Monoclinic
$P2_1/c$
a = 13.800 (6) Å
b = 7.406 (1) Å
c = 16.114 (3) Å
β = 106.04 (2)°
V = 1582.8 (8) Å^3
Z = 4
D_x = 1.366 Mg m^{-3}
D_m = 1.37 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.5418 Å
Cell parameters from 25 reflections
θ = 12.5–25.0°
μ = 0.306 mm^{-1}
T = 295 K
Tablet
0.6 × 0.3 × 0.1 mm
Pale yellow

Data collection

Rigaku AFC-4 diffractometer
ω–2θ scans
Absorption correction: none
2569 measured reflections
2460 independent reflections
1652 observed reflections [$I \geq 3\sigma(I)$]
R_{int} = 0.023
θ_{max} = 61.5°
$h = -15 \rightarrow 14$
$k = 0 \rightarrow 8$
$l = 0 \rightarrow 18$
3 standard reflections monitored every 50 reflections
intensity decay: not significant

Refinement

Refinement on F
R = 0.052
wR = 0.058
S = 0.882
1652 reflections
256 parameters
Only coordinates of H atoms refined
$w = 1/[\sigma^2(F_o) + 0.0068F_o^2]$
$(\Delta/\sigma)_{max}$ = 0.036
$\Delta\rho_{max}$ = 0.29 e Å^{-3}
$\Delta\rho_{min}$ = −0.41 e Å^{-3}
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

Table 1. *Fractional atomic coordinates and equivalent isotropic displacement parameters* (Å^2)

$U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
S(1)	−0.0442 (1)	0.4745 (2)	0.3652 (1)	0.042 (1)
C(2)	0.0735 (3)	0.5436 (6)	0.3596 (3)	0.036 (1)
N(3)	0.0762 (2)	0.7269 (5)	0.3636 (2)	0.033 (1)
C(4)	−0.0105 (3)	0.8107 (6)	0.3740 (3)	0.032 (1)
C(5)	−0.0827 (3)	0.6923 (6)	0.3768 (3)	0.034 (1)
S(2α)	0.1642 (1)	0.4035 (2)	0.3519 (1)	0.057 (1)
C(4α)	−0.0134 (4)	1.0116 (7)	0.3794 (4)	0.051 (2)
C(5α)	−0.1846 (3)	0.7262 (7)	0.3918 (3)	0.042 (2)
C(5β)	−0.2729 (3)	0.6911 (7)	0.3123 (3)	0.045 (2)
O(5γ)	−0.2717 (2)	0.5153 (5)	0.2770 (2)	0.046 (1)
C(3,5′)	0.1699 (3)	0.8239 (7)	0.3654 (3)	0.039 (1)
N(1′)	0.2818 (3)	0.7614 (5)	0.6060 (2)	0.040 (1)
C(2′)	0.3701 (3)	0.8422 (7)	0.6140 (3)	0.037 (1)
N(3′)	0.4017 (3)	0.9140 (5)	0.5506 (2)	0.039 (1)
C(4′)	0.3380 (3)	0.9097 (6)	0.4701 (3)	0.033 (1)
C(5′)	0.2410 (3)	0.8321 (6)	0.4550 (3)	0.032 (1)
C(6′)	0.2185 (3)	0.7604 (6)	0.5262 (3)	0.035 (1)
C(2′α)	0.4419 (4)	0.8476 (9)	0.7036 (3)	0.056 (2)
N(4′α)	0.3721 (3)	0.9744 (6)	0.4065 (3)	0.046 (1)
C(1*A*)	0.432 (2)	0.427 (3)	0.504 (2)	0.119 (9)
C(2*A*)	0.5246 (19)	0.523 (3)	0.5354 (11)	0.110 (6)
C(3*A*)	0.5809 (16)	0.601 (4)	0.4739 (19)	0.089 (7)
O(*A*)	0.5543 (13)	0.546 (3)	0.6084 (12)	0.179 (7)

Table 2. *Selected geometric parameters* (Å, °)

S(1)—C(2)	1.729 (4)	S(1)—C(5)	1.724 (5)
C(2)—N(3)	1.360 (6)	C(2)—S(2α)	1.656 (4)
N(3)—C(4)	1.398 (5)	N(3)—C(3,5′)	1.473 (5)
C(4)—C(5)	1.337 (6)	C(4)—C(4α)	1.492 (7)
C(5)—C(5α)	1.513 (6)	C(5α)—C(5β)	1.526 (6)
C(5β)—O(5γ)	1.422 (6)	C(3,5′)—C(5′)	1.506 (6)
N(1′)—C(2′)	1.332 (6)	N(1′)—C(6′)	1.340 (6)
C(2′)—N(3′)	1.327 (6)	C(2′)—C(2′α)	1.508 (7)
N(3′)—C(4′)	1.352 (6)	C(4′)—C(5′)	1.415 (6)
C(4′)—N(4′α)	1.328 (6)	C(5′)—C(6′)	1.376 (6)
C(1*A*)—C(2*A*)	1.43 (4)	C(2*A*)—C(3*A*)	1.53 (3)
C(2*A*)—O(*A*)	1.15 (3)		
N(3)—C(2)—S(1)	107.8 (3)	C(4)—N(3)—C(2)	115.9 (3)
C(4)—C(5)—S(1)	110.8 (3)	C(5)—S(1)—C(2)	92.9 (2)
C(5)—C(4)—N(3)	112.5 (4)	S(2α)—C(2)—S(1)	124.0 (3)
S(2α)—C(2)—N(3)	128.2 (3)	C(4α)—C(4)—N(3)	119.2 (4)
C(4α)—C(4)—C(5)	128.3 (4)	C(5α)—C(5)—S(1)	120.0 (3)

C(5α)—C(5)—C(4)	129.1 (4)	C(5β)—C(5α)—C(5)	113.6 (4)
O(5γ)—C(5β)—C(5α)	113.3 (4)	C(3,5′)—N(3)—C(2)	120.0 (3)
C(3,5′)—N(3)—C(4)	123.9 (4)	N(3′)—C(2′)—N(1′)	126.3 (4)
C(4′)—N(3′)—C(2′)	117.8 (4)	C(4′)—C(5′)—C(3,5′)	121.0 (4)
C(5′)—C(3,5′)—N(3)	112.0 (4)	C(5′)—C(4′)—N(3′)	120.5 (4)
C(5′)—C(6′)—N(1′)	124.1 (4)	C(6′)—N(1′)—C(2′)	115.6 (4)
C(6′)—C(5′)—C(3,5′)	123.1 (4)	C(6′)—C(5′)—C(4′)	115.7 (4)
C(2′α)—C(2′)—N(1′)	116.5 (4)	C(2′α)—C(2′)—N(3′)	117.2 (4)
N(4′α)—C(4′)—N(3′)	117.2 (4)	N(4′α)—C(4′)—C(5′)	122.3 (4)
C(1A)—C(2A)—C(3A)	122. (2)	O(A)—C(2A)—C(1A)	118 (2)
O(A)—C(2A)—C(3A)	120 (2)		

Table 3. *Hydrogen-bonding geometry* (Å, °)

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N(4′α)—H(1)···O(5γ^{i})	1.97 (5)	2.915 (5)	173 (5)
N(4′α)—H(2)···N(3′^{ii})	2.26 (5)	3.117 (5)	165 (5)
O(5γ)—H···N(1′^{iii})	1.95 (5)	2.814 (4)	176 (5)

Symmetry codes: (i) $-x, \frac{1}{2}+y, \frac{1}{2}-z$; (ii) $1-x, 2-y, 1-z$; (iii) $-x, 1-y, 1-z$.

The structure was solved by direct methods and refined by full-matrix least squares using *SHELX*76 (Sheldrick, 1976). A difference map after anisotropic refinement of the TTT molecule revealed the peaks for all H atoms of TTT and additional prominent peaks near the inversion centre at $(\frac{1}{2},\frac{1}{2},\frac{1}{2})$. These peaks were identified, with difficulty, as the disordered acetone solvate, based on the interpretation of the geometrical relationships of the peaks, the NMR spectra and the elemental analysis data of the crystal. In the final cycle of refinement, each H atom was assigned a fixed isotropic displacement parameter 1.3 times greater than the isotropic equivalent of the atom to which it is attached. H atoms in the acetone molecule could not be located and were not included in the structure-factor calculations.

This work was supported by a grant from the Korea Science and Engineering Foundation.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and bond distances and angles involving H atoms have been deposited with the IUCr (Reference: HR1001). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Acta Cryst. (1995). C**51**, 318–322

The Novel $GABA_A$ Receptor Ligand NNC 14-0764: 5-(3-Cyclopropyl-1,2,4-oxadiazol-5-yl)-2,3-dihydrodiimidazo[1,5-*a*:1′,2′-*c*]-quinazoline

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(*Received* 28 *February* 1994; *accepted* 19 *April* 1994)

Abstract

The crystal and molecular structure of the title compound, $C_{17}H_{14}N_6O$, has been determined. The two molecules in the asymmetric unit have very similar geometrical features, the major difference being in the overall convex or concave shape of the molecular surface. As a consequence, although as expected, the cyclopropyl rings are approximately perpendicular to the general molecular plane; the three C atoms of the cyclopropyl groups are distributed quite differently above and below the general molecular plane in the two molecules. Consequences of this effect for theoretical consideration of drug activity are discussed.