Table 2. *Selected torsion angles (°) for (2)*

O101—C117—C118—C123	175.4 (4)
C118—C117—O101—C116	177.6 (3)
C105—C116—O101—C117	−144.6 (3)
C205—C216—O201—C217	116.0 (3)
C216—O201—C217—C218	178.4 (3)
C223—C218—C217—O201	−165.6 (3)
O301—C317—C318—C323	−172.7 (3)
C318—C317—O301—C316	−175.1 (3)
C305—C316—O301—C317	−153.4 (3)

Table 3. *Hydrogen-bonding geometry (Å, °) for (2)*

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
O400—H400···O107	0.82	2.253	3.023 (19)	156.3
O403—H403···O305^{i}	0.82	2.175	2.997 (14)	171.5

Symmetry code: (i) $1+x, y, z$.

For compound (2), the disordered ester was split into two partially occupied groups with 50% occupancy factors. All disordered atoms were refined isotropically. The *SAME* and *SADI* restraints in *SHELXL*93 (Sheldrick, 1993) were applied for refinement. The ethanol solvent-occupancy refinement converged to 0.46 (1) and 0.30 (1) for O400—C401—C402 and O403—C404—C405, respectively. A restrain refinement was applied using the *SAME* and *SADI* options. All H atoms were geometrically placed. The O—H and C—H distances were set to 0.82 and 0.93–0.98 Å, respectively. The highest and lowest residual densities for (2) were located in the vicinity of the Br atoms.

For both compounds, data collection: *NRCCAD DATCOL* (Le Page, White & Gabe, 1986); cell refinement: *NRCCAD TRUANG*; data reduction: *NRCVAX DATRD2* (Gabe, Le Page, Charland, Lee & White, 1989). Program(s) used to solve structures: *NRCVAX SOLVER* for (1); *SIR*92 (Altomare, Cascarano, Giacovazzo & Guargliardi, 1993) for (2). Program(s) used to refine structures: *NRCVAX LSTSQ* for (1); *SHELXL*93 (Sheldrick, 1993) for (2). For both compounds, molecular graphics: *ORTEP* in *Xtal_GX* (Johnson, 1995). Software used to prepare material for publication: *NRCVAX TABLES* for (1); *SHELXL*93 *ACTA* for (2).

Supplementary data for this paper are available from the IUCr electronic archives (Reference: FG1245). Services for accessing these data are described at the back of the journal.

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Acta Cryst. (1997). C**53**, 1493–1495

Methyl 12-Acetyl-9-methyl-11-thioxo-8-oxa-10,12-diazatricyclo[7.3.1.0^{2,7}]trideca-2,4,6-triene-13-carboxylate

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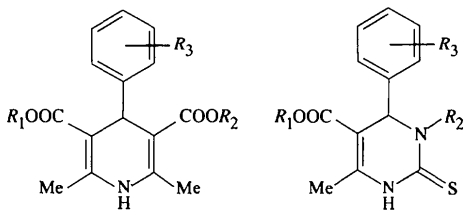
Abstract

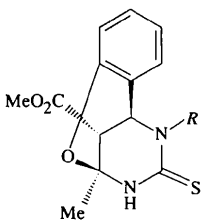
The title compound, $C_{15}H_{16}N_2O_4S$, represents a conformationally restricted dihydropyrimidine analogue of 1,4-dihydropyridine-type calcium antagonists and was selected for a crystal structure determination in order to clarify some aspects of structure–activity relationships. The carbonyl function of the acetyl group is oriented *cis* with respect to the C2—N3 bond, presumably to avoid repulsive interaction between the negatively charged carbonyl O and thione S atoms.

Comment

The 1,4-dihydropyridines, (1), are known to be the most potent class of calcium-channel antagonists widely used in clinical medicine. However, these compounds have a serious disadvantage in that their plasma half-lives are relatively short due to their rapid metabolic oxidation to inactive pyridines. In an effort to prolong their duration of action, new drugs based on a dihydropyrimidine-2-thione substructure, (2), have been developed (Rovnyak *et al.*, 1992). Although the pyrimidine nucleus is stable against oxidation, the vasorelaxant activity of molecules of type (2) was reported to be generally three to five times lower compared to that of type (1). For derivative (2*a*), this was confirmed in both *in vitro* and radioligand-binding experiments (Kettmann, Dřímal &

Svetlík, 1996). To gain further insight into the structure–activity relationships, we undertook an X-ray analysis of the title compound, (2*b*), and compared the results with those obtained previously for 1,4-dihydropyridines.





(2*a*) *R* = H
(2*b*) *R* = Acetyl

As shown in Table 1, bond lengths and angles within the central dihydropyrimidine ring are affected by conjugation. The formal single bonds N1—C2, C2—N3 and N1—C6 have partial double-bond character and are all shorter than the essentially pure single bonds N1—C6 and N3—C4 (Burke-Laing & Laing, 1976). Moreover, the sum of the valence angles around the N1 and N3 atoms is close to 360°, indicating that the state of hybridization of these atoms is sp^2. These data are consistent with π-electron delocalization from the heterocyclic N atoms into the carbonyl and thione groups, leading to the development of negative charges on the O2 and S1 atoms.

As noted above, the aim of this study was to identify the structural feature(s) responsible for the loss of the vasorelaxant activity of compounds of (2) relative to (1). It is known that the activity is dependent on the relative disposition of the essential pharmacophoric elements, *i.e.* NH moiety, 4-phenyl ring and equatorial alkyl(alkoxy)carbonyl groups, which in turn is determined by the conformation of the central heterocycle (Goldmann & Stoltefuss, 1991). Calculation of the least-squares planes has shown that the ring is puckered in such a manner that the four atoms C6, N1, C2 and N3 are coplanar to within 0.025 (3) Å, and the atoms C4 and C5 are displaced from this plane on opposite sides, with out-of-plane displacements of −0.469 (4) and 0.390 (3) Å, respectively. Thus, the dihydropyrimidine ring exhibits a slightly unsymmetrical half-chair conformation and exists in the thione form: the C2—S1 distance of 1.666 (3) Å has essentially double-bond character (Abrahams, 1956). Such a conformation is not very different from the flattened boat conformation generally found for the classical 1,4-dihydropyridines, (1). Moreover, the 4-phenyl ring in (2*b*) is fixed in the bioactive conformation by the oxygen bridge, *i.e.* it is in a perpendicular orientation with respect to the mean plane of the dihydropyrimidine ring [dihedral angle 89.2 (3)°].

As a consequence of the conjugation described earlier, the acetyl group on N3 lies approximately in the plane defined by atoms N1, C2, S1 and N3, and the carbonyl group C13—O2 is oriented *trans* relative to the C2—N3 bond. This is in marked contrast to 1,4-dihydropyridines for which a *cis* conformation of the carbonyl group is favoured, as revealed by a number of X-ray structure determinations (Goldmann & Stoltefuss, 1991). Obviously, the different conformations of the carbonyl group result from the interaction between the carbonyl O atom and the substituent at C2: in (1), the interaction is attractive due to the presence of the 2-methyl group and becomes repulsive upon introduction of the negatively charged thione S atom. It is generally accepted that the carbonyl O atom is able to form a hydrogen bond with the binding site when it is in the *cis* orientation. Thus, the acetyl group in (2*b*) must be rotated at the receptor by *ca* 180° into the less favourable (*cis*) conformation, leading to some loss of affinity for the dihydropyridine receptor. There is a short intermolecular contact N1—H1···S1($1-x, -y, 1-z$), which, based on its geometry, can be regarded as a hydrogen-bond interaction [N—H 0.844 (2), N···S 3.394 (3), H···S 2.560 (1) Å and N—H···S 170.0 (1)°]. Thus, the molecules associate in pairs to form hydrogen-bonded dimers across the centre of symmetry at $\frac{1}{2},0,\frac{1}{2}$. The dimers are packed by van der Waals interactions.

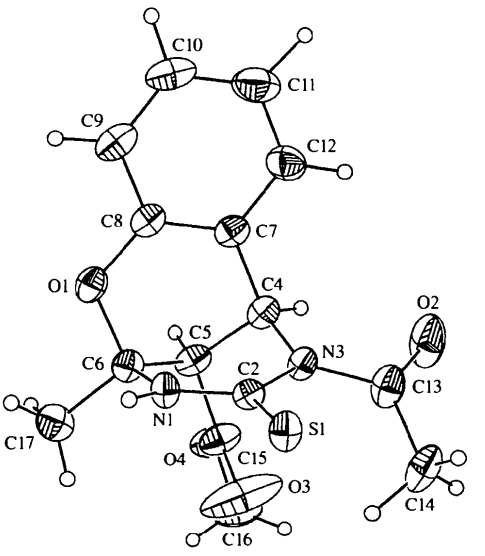


Fig. 1. A view (*ORTEPII*; Johnson, 1976) of the title molecule, showing the labelling of the non-H atoms. Displacement ellipsoids are drawn at the 50% probability level; H atoms are drawn as small circles of arbitrary radii.

Experimental

The *N*-acetyl derivative (2*b*) was prepared from the parent O-bridged pyrimidine (2*a*) (Kettmann & Svetlík, 1996) by acetylation with acetic anhydride, as described by Kettmann, Dřímal & Svetlík (1996).

Crystal data

$C_{15}H_{16}N_2O_4S$
$M_r = 320.36$
Triclinic
$P\bar{1}$
$a = 8.962\,(3)$ Å
$b = 9.651\,(4)$ Å
$c = 10.009\,(4)$ Å
$\alpha = 68.45\,(3)°$
$\beta = 71.46\,(3)°$
$\gamma = 81.52\,(3)°$
$V = 762.9\,(5)$ Å^3
$Z = 2$
$D_x = 1.395$ Mg m^{-3}
$D_m = 1.40\,(1)$ Mg m^{-3}
D_m measured by flotation in bromoform–hexane
Mo $K\alpha$ radiation
$\lambda = 0.71073$ Å
Cell parameters from 15 reflections
$\theta = 8$–$18°$
$\mu = 0.232$ mm^{-1}
$T = 293\,(2)$ K
Prism
0.35 × 0.25 × 0.20 mm
Colourless

Data collection

Syntex $P2_1$ diffractometer
$\theta/2\theta$ scans
Absorption correction: none
2893 measured reflections
2715 independent reflections
2008 reflections with $I > 2\sigma(I)$
$R_{int} = 0.031$
$\theta_{max} = 25.06°$
$h = 0 \rightarrow 10$
$k = -11 \rightarrow 11$
$l = -10 \rightarrow 11$
2 standard reflections
frequency: 100 min
intensity decay: none

Refinement

Refinement on F^2
$R[F^2 > 2\sigma(F^2)] = 0.051$
$wR(F^2) = 0.113$
$S = 1.132$
2715 reflections
200 parameters
H atoms not refined
$w = 1/[\sigma^2(F_o^2) + (0.0905P)^2 + 0.4132P]$ where $P = (F_o^2 + 2F_c^2)/3$
$(\Delta/\sigma)_{max} = 0.028$
$\Delta\rho_{max} = 0.623$ e Å^{-3}
$\Delta\rho_{min} = -0.472$ e Å^{-3}
Extinction correction: *SHELXL*93 (Sheldrick, 1993)
Extinction coefficient: 0.002 (5)
Scattering factors from *International Tables for Crystallography* (Vol. C)

Table 1. *Selected geometric parameters (Å, °)*

S1—C2	1.666 (3)	C4—C7	1.492 (4)
N1—C2	1.322 (3)	C4—C5	1.514 (4)
N1—C6	1.456 (3)	C5—C6	1.518 (4)
C2—N3	1.366 (3)	C6—O1	1.426 (3)
N3—C13	1.411 (4)	C8—O1	1.365 (4)
N3—C4	1.472 (3)	C13—O2	1.199 (4)
C2—N1—C6	129.1 (2)	N3—C4—C5	107.8 (2)
N1—C2—N3	116.2 (2)	C4—C5—C6	105.0 (2)
N1—C2—S1	120.5 (2)	N1—C6—C5	109.1 (2)
N3—C2—S1	123.1 (2)	C8—O1—C6	115.5 (2)
C2—N3—C13	126.3 (2)	O2—C13—N3	117.6 (3)
C2—N3—C4	116.3 (2)	O2—C13—C14	121.5 (3)
C13—N3—C4	117.0 (2)	N3—C13—C14	120.7 (3)
C6—N1—C2—N3	6.8 (4)	N3—C4—C5—C6	67.8 (3)
C6—N1—C2—S1	−177.7 (2)	C2—N1—C6—C5	10.4 (4)
N1—C2—N3—C13	−156.5 (3)	C4—C5—C6—N1	−45.8 (3)
N1—C2—N3—C4	16.1 (3)	C2—N3—C13—O2	−161.9 (3)
C2—N3—C4—C5	−54.4 (3)		

All H atoms were located in difference maps and were not refined, with U_{iso} set to $1.2U_{eq}$ of the parent atom.

Data collection: Syntex $P2_1$ diffractometer software. Cell refinement: Syntex $P2_1$ diffractometer software. Data reduction: *XP*21 (Pavelčík, 1987). Program(s) used to solve structure: *SHELXS*86 (Sheldrick, 1985). Program(s) used to refine structure: *SHELXL*93 (Sheldrick, 1993). Molecular graphics: *ORTEP*II (Johnson, 1976). Software used to prepare material for publication: *SHELXL*93.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: SK1098). Services for accessing these data are described at the back of the journal.

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The Cone Conformer of a Tetrakis(methylthio)tetrapropoxycalix[4]arene

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Abstract

5,11,17,23-Tetrakis(methylthio)-25,26,27,28-tetrapropoxycalix[4]arene, $C_{44}H_{56}O_4S_4$, adopts a 'distorted-cone' conformation in the solid state. This distortion