

Dimorphism in (2*Z*)-2-benzylidene-*N*,7-dimethyl-3-oxo-5-phenyl-2,3-dihydro-5*H*-1,3-thiazolo[3,2-*a*]-pyrimidine-6-carboxamide

B. Sridhar,^{a*} K. Ravikumar^a and Y. S. Sadanandam^b

^aLaboratory of X-ray Crystallography, Indian Institute of Chemical Technology, Hyderabad 500 007, India, and ^bOrganic Division, Indian Institute of Chemical Technology, Hyderabad 500 007, India
Correspondence e-mail: sshiya@yahoo.com

Received 16 October 2006

Accepted 6 November 2006

Online 22 November 2006

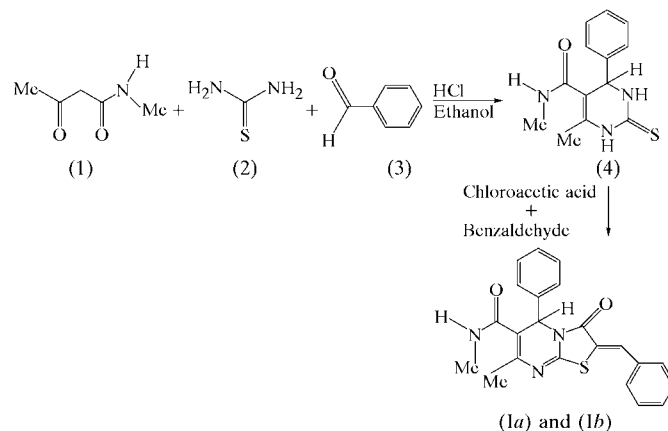
The title compound, C₂₂H₁₉N₃O₂S, crystallizes in two polymorphic forms having the same space group, *viz.* *P* $\bar{1}$, with *Z'* = 2 and *Z'* = 1. In both polymorphs, the planar thiazole ring is fused *cis* with the dihydropyrimidine ring, the carbamoyl group is in an extended conformation with an anticlinal orientation with respect to the pyrimidine ring, and the phenyl ring is attached to the pyrimidine ring approximately at a right angle. The two polymorphs have different interplanar angles between the phenyl and thiazole rings. The molecules are linked by N—H...O and C—H...O hydrogen bonds.

Comment

Dihydropyrimidines (DHPMs) are heterocyclic systems of remarkable pharmacological potency with antiviral, anti-tumour, antibacterial and anti-inflammatory activities, and they are used as calcium channel modulators and anti-hypertensive agents (Kappe, 2000; Rovnyak *et al.*, 1995). DHPMs exhibit a similar pharmacological profile to DHP calcium channel modulators of the nifedipine type and much activity has been observed in this area (Kappe, 1993; Atwal *et al.*, 1991). A DHPM analogue has recently been identified as a potential new anticancer lead that is involved in blocking mitosis by inhibition of a kinesin motor protein (Mayer *et al.*, 1999). We have reported a series of DHPM crystal structures (Ravikumar & Sridhar, 2005; Sridhar & Ravikumar, 2005*a,b*) and now report the crystal structures of two triclinic polymorphs, (Ia) and (Ib), of the title compound.

The two polymorphs crystallize in the same space group, *viz.* *P* $\bar{1}$, but there are two independent but chemically identical molecules (1 and 2) in the asymmetric unit of form (Ia) (Fig. 1), whereas there is only one in form (Ib) (Fig. 2). The pyrimidine rings in (Ia) and (Ib) have a chiral C atom at the point of attachment of the phenyl group. Since both compounds crystallize in a centrosymmetric space group, in the solid state a racemic mixture was obtained from the synthesis. It has been

reported (Atwal *et al.*, 1990) that the critical factor for the biological activity of most DHPMs is the absolute stereochemistry at the C5 stereocentre. The bond distances and



angles in (Ia) and (Ib) (Tables 1 and 3) are in normal ranges (Allen *et al.*, 1987) and are comparable with the corresponding values observed in similar structures (Sulmon *et al.*, 1989; Chandra Mohan *et al.*, 2003; Liang & Cao, 2004). The molecular geometries of the two independent molecules in (Ia) are very similar; the largest differences are 0.012 (4) Å for the C24—C25 bond distance and 1.1 (2)° for the C2—C21—C22 angle. The bond distances involving the S atom, *viz.* C2—S1 and C9—S1, are significantly different [0.01 (2) Å]. In polymorph (Ib), the benzylidene C22—C27 phenyl ring is disordered (all atoms except C22) over two sites of equal occupancy (Fig. 2).

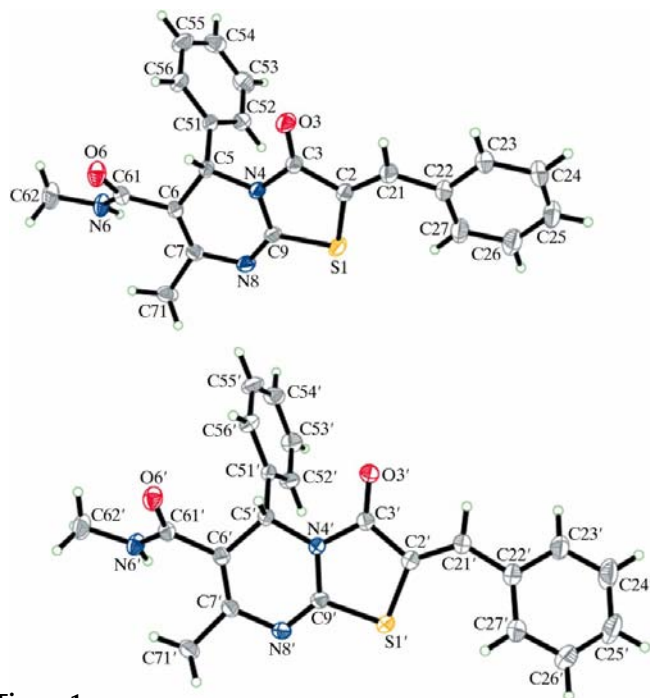


Figure 1
Perspective views of the two independent molecules of polymorph (Ia), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

Each molecule consists of a fused thiazolo[3,2-*a*]pyrimidine ring system with a carbamoyl group and two substituent phenyl groups. It is interesting to note that the thiazole ring cyclization, with respect to the central pyrimidine ring, preferentially occurs with N4 (linear fusion) over N8 (angular fusion), perhaps facilitated by the simultaneous formation of conjugated double bonds. As observed in a similar thiazole–pyrimidine structure (Liu *et al.*, 2004), the thiazole and pyrimidine rings are only approximately coplanar in both polymorphs, with maximum deviations of 0.161 (2) Å for atom C5 of molecule 1 of (*Ia*), −0.042 (2) Å for atom C7 of molecule 2 of (*Ia*) and −0.084 (3) Å for atom C7 of (*Ib*) with respect to the least-squares planes defined by atoms S1/C2/C3/N4/C5–C7/N8/C9 of the ring system. The interplanar angles between the pyrimidine and thiazole rings are 6.1 (2)° for molecule 1 of (*Ia*), 2.8 (1)° for molecule 2 of (*Ia*) and 4.2 (1)° for (*Ib*).

The carbamoyl side chain is in a fully extended conformation. The spatial arrangement of the carbonyl group at C6 adopts an anticlinal (*ac*) orientation about the C6–C61 bond (Tables 1 and 3). This orientation can probably be attributed to intermolecular N–H⋯O hydrogen bonding involving

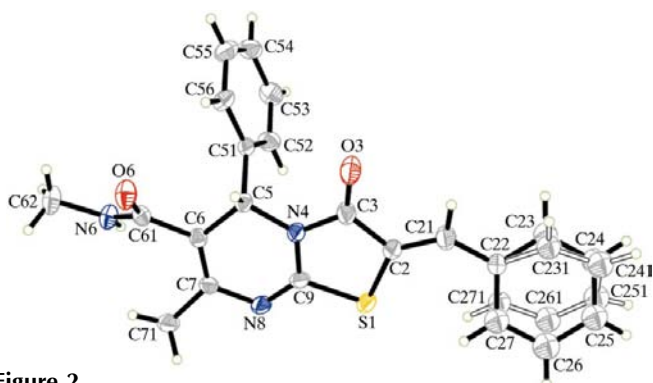


Figure 2
A perspective view of the molecule of polymorph (*Ib*), showing the atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radii.

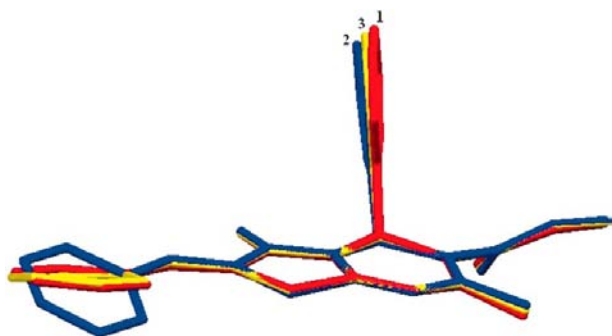


Figure 3
The least-squares fit between molecule 1 of polymorph (*Ia*) (labelled 1), molecule 2 of polymorph (*Ia*) (labelled 2) (r.m.s. deviation = 0.062 Å) and the molecule of polymorph (*Ib*) (labelled 3) (r.m.s. deviation = 0.031 Å). The disordered atoms of the minor component (C121–C161) and all H atoms have been omitted for clarity.

atom N6 and carbonyl atom O6 of the carbamoyl side chain for both polymorphs. The phenyl rings [*e.g.* C51–C56 in (*Ia*)] are oriented approximately perpendicular to the pyrimidine ring, as shown by the torsion angle C6–C5–C51–C52 (Tables 1 and 3). Specifically, the interplanar angles are 79.8 (1)° for molecule 1 of (*Ia*), 78.2 (2)° for molecule 2 of (*Ia*) and 78.6 (1)° for (*Ib*).

A significant difference is observed in the orientation of the benzylidene C22–C27 phenyl ring with respect to the thiazole ring between the two independent molecules of (*Ia*) and in (*Ib*) (Fig. 3). The interplanar angles between the mean planes of the phenyl and thiazole rings are 10.2 (2) and 23.4 (2)°, respectively, for molecules 1 and 2 in (*Ia*), and 29.5 (2) and 15.4 (1)° for the two disordered components of (*Ib*). The disposition of the C9=C10 double bond with respect to the phenyl ring affords the possibility of *E* and *Z* isomers. Both polymorphs contain *Z* isomers, as shown by the C2–C21–C22–C23 torsion angle (Tables 1 and 3). The dihedral angles between the two phenyl rings are 84.3 (1) and 64.3 (1)°, respectively, for molecules 1 and 2 in (*Ia*), and 61.4 (2) and 85.2 (2)° for the two disordered components in (*Ib*).

In both polymorphs (*Ia*) and (*Ib*), the crystal structure is stabilized by N–H⋯O, C–H⋯O and C–H⋯S hydrogen bonds (Tables 2 and 4). A weak intramolecular C–H⋯S hydrogen bond forms a pseudo-six-membered ring of an *S*(6)-type motif (Bernstein *et al.*, 1995) in both polymorphs. The molecules of (*Ia*) are linked by a combination of N–H⋯O

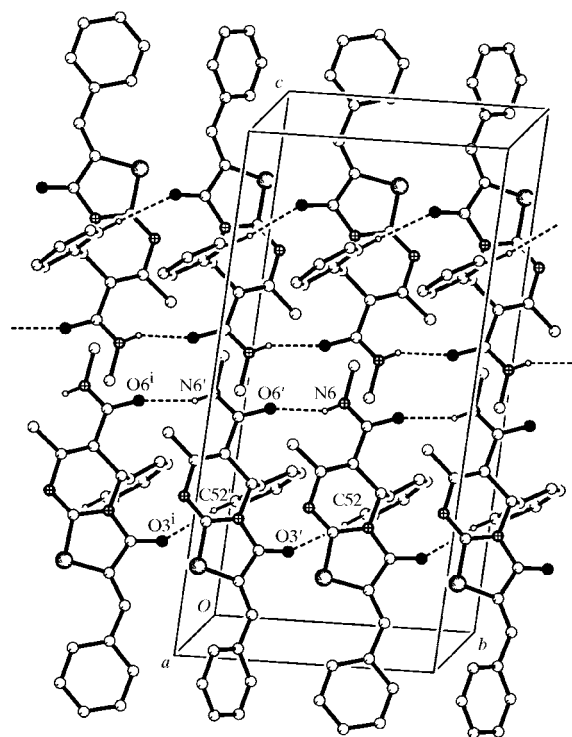


Figure 4
A part of the crystal structure of polymorph (*Ia*), showing the infinite chain along the *b* axis. Dashed lines indicate N–H⋯O and C–H⋯O hydrogen bonds. For the sake of clarity, H atoms not involved in hydrogen bonding have been omitted. Only atoms involved in hydrogen bonding are labelled. [Symmetry code: (i) *x*, *y* − 1, *z*.]

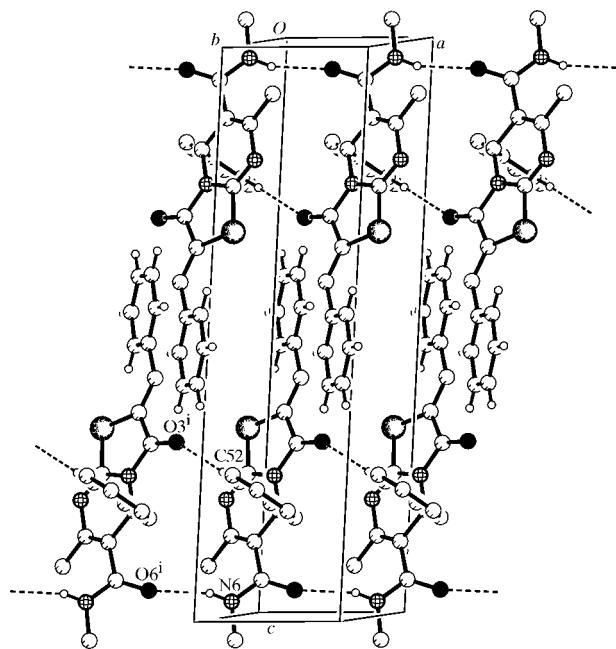


Figure 5

A part of the crystal structure of polymorph (Ib), showing the infinite chain along the *a* axis. Dashed lines indicate N—H...O and C—H...O hydrogen bonds. For the sake of clarity, the disordered atoms of the minor component (C121–C161) and all H atoms not involved in hydrogen bonding have been omitted. Only atoms involved in hydrogen bonding are labelled. [Symmetry code: (i) $x - 1, y, z$.]

and C—H...O hydrogen bonds (Table 2). Within the asymmetric unit, atom N6 acts as hydrogen-bond donor, *via* atom H6N, to atom O6'. In a similar manner, atom N6' at (*x*, *y*, *z*) acts as donor, *via* atom H6N', to atom O6 at (*x*, *y* − 1, *z*). These N—H...O hydrogen bonds lead to the formation of an infinite chain of C(4)-type motifs, running along the crystallographic *b* axis (Fig. 4). In a similar fashion, C—H...O interactions involving atom C52 of the phenyl ring and atom O3 of the thiazole ring form an infinite chain running along the *b* axis. In (Ib), atoms N6 and C52 act as hydrogen-bond donors to atoms O6 and O3 (Table 4) thereby generating a C(4)-type motif of chains running along the crystallographic *a* axis (Fig. 5).

The hydrogen-bond networks thus formed facilitate alternating hydrophobic and hydrophilic zones in both polymorphs. In polymorph (Ia), the hydrophobic layers around the $b = \frac{1}{4}$ and $b = \frac{3}{4}$ axes are sandwiched between the hydrophilic layers about $b = 0$ and $b = 1$, while in polymorph (Ib), the hydrophobic layers around $a = \frac{1}{2}$ are sandwiched between the hydrophilic layers about $a = 0$ and $a = 1$.

Experimental

A mixture of *N*-methylacetoacetamide, (1) (100 mmol), thiourea, (2) (100 mmol), benzaldehyde, (3) (100 mmol), absolute ethanol (50 ml) and concentrated hydrochloric acid (2 ml) was stirred and warmed slightly over a steam bath until the mixture become a clear solution. It was allowed to stand overnight at room temperature. The pyrimidinethione thus formed, (4), was filtered off and dried. A

mixture of (4) (5.2 g, 2 mmol), chloroacetic acid (2 g, 2 mmol), benzaldehyde (2 g, 2 mmol), fused sodium acetate (4 g, 5 mmol), acetic acid (20 ml) and acetic anhydride (8 ml) was refluxed for 1 h, cooled and poured into cold water. The suspended solid was dissolved in diethyl ether and then treated with petroleum ether (313–333 K) to give a yellow solid, which was recrystallized from dimethylformamide. Crystals of polymorph (Ia) suitable for X-ray analysis were obtained by slow evaporation of a dimethylformamide solution and those of polymorph (Ib) were obtained from a methanol solution.

Polymorph (Ia)

Crystal data

$C_{22}H_{19}N_3O_2S$
 $M_r = 389.46$
 Triclinic, $P\bar{1}$
 $a = 9.5353$ (6) Å
 $b = 10.2071$ (6) Å
 $c = 20.7901$ (12) Å
 $\alpha = 79.198$ (1)°
 $\beta = 79.645$ (1)°
 $\gamma = 78.257$ (1)°

$V = 1924.8$ (2) Å³
 $Z = 4$
 $D_x = 1.344$ Mg m^{−3}
 Mo $K\alpha$ radiation
 $\mu = 0.19$ mm^{−1}
 $T = 293$ (2) K
 Needle, pale yellow
 $0.20 \times 0.11 \times 0.08$ mm

Data collection

Bruker SMART APEX CCD area-detector diffractometer
 ω scans
 14058 measured reflections

6733 independent reflections
 5389 reflections with $I > 2\sigma(I)$
 $R_{int} = 0.021$
 $\theta_{max} = 25.0^\circ$

Refinement

Refinement on F^2
 $R[F^2 > 2\sigma(F^2)] = 0.053$
 $wR(F^2) = 0.141$
 $S = 1.06$
 6733 reflections
 517 parameters
 H atoms treated by a mixture of independent and constrained refinement

$w = 1/[\sigma^2(F_o^2) + (0.0671P)^2 + 0.5641P]$
 where $P = (F_o^2 + 2F_c^2)/3$
 $(\Delta/\sigma)_{max} = 0.001$
 $\Delta\rho_{max} = 0.34$ e Å^{−3}
 $\Delta\rho_{min} = -0.15$ e Å^{−3}

Table 1

Selected geometric parameters (Å, °) for polymorph (Ia).

C2—S1	1.748 (2)	C2'—S1'	1.746 (2)
C9—S1	1.755 (2)	C9'—S1'	1.755 (2)
C24—C25	1.377 (4)	C24'—C25'	1.365 (4)
C2—C21—C22	131.1 (2)	C2'—C21'—C22'	130.0 (2)
C2—C21—C22—C27	4.3 (4)	C2'—C21'—C22'—C27'	−20.2 (4)
C2—C21—C22—C23	−179.4 (2)	C2'—C21'—C22'—C23'	161.8 (3)
C6—C5—C51—C52	−79.0 (2)	C6'—C5'—C51'—C52'	−77.4 (2)
C7—C6—C61—O6	135.6 (2)	C7'—C6'—C61'—O6'	131.5 (2)
C6—C61—N6—C62	177.0 (2)	C6'—C61'—N6'—C62'	175.3 (2)

Table 2

Hydrogen-bond geometry (Å, °) for polymorph (Ia).

D—H...A	D—H	H...A	D...A	D—H...A
N6—H6N...O6'	0.82 (2)	2.17 (2)	2.939 (3)	157 (2)
N6'—H6N'...O6 ⁱ	0.80 (2)	2.16 (2)	2.922 (3)	161 (2)
C27—H27...S1	0.93	2.55	3.255 (3)	133
C27'—H27'...S1'	0.93	2.63	3.267 (3)	126
C52—H52...O3 ⁱ	0.93	2.31	3.193 (3)	160
C52'—H52'...O3 ⁱ	0.93	2.32	3.247 (3)	173

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

Polymorph (Ib)

Crystal data

$C_{22}H_{19}N_3O_2S$	$V = 968.0 (3) \text{ \AA}^3$
$M_r = 389.46$	$Z = 2$
Triclinic, $P\bar{1}$	$D_x = 1.336 \text{ Mg m}^{-3}$
$a = 5.1109 (9) \text{ \AA}$	Mo $K\alpha$ radiation
$b = 9.5564 (16) \text{ \AA}$	$\mu = 0.19 \text{ mm}^{-1}$
$c = 20.503 (3) \text{ \AA}$	$T = 293 (2) \text{ K}$
$\alpha = 97.594 (3)^\circ$	Block, pale yellow
$\beta = 93.371 (3)^\circ$	$0.20 \times 0.17 \times 0.12 \text{ mm}$
$\gamma = 101.755 (3)^\circ$	

Data collection

Bruker SMART APEX CCD area-detector diffractometer	3395 independent reflections
ω scans	2656 reflections with $I > 2\sigma(I)$
9402 measured reflections	$R_{\text{int}} = 0.037$
	$\theta_{\text{max}} = 25.0^\circ$

Refinement

Refinement on F^2	$w = 1/[\sigma^2(F_o^2) + (0.0565P)^2 + 0.3108P]$
$R[F^2 > 2\sigma(F^2)] = 0.067$	where $P = (F_o^2 + 2F_c^2)/3$
$wR(F^2) = 0.161$	$(\Delta/\sigma)_{\text{max}} < 0.001$
$S = 1.28$	$\Delta\rho_{\text{max}} = 0.43 \text{ e \AA}^{-3}$
3395 reflections	$\Delta\rho_{\text{min}} = -0.30 \text{ e \AA}^{-3}$
254 parameters	
H atoms treated by a mixture of independent and constrained refinement	

Table 3

Selected geometric parameters (\AA , $^\circ$) for polymorph (Ib).

C2—S1	1.741 (3)	C24—C25	1.3899 (11)
C9—S1	1.759 (3)		
C2—C21—C22	132.4 (3)		
C2—C21—C22—C27	−29.9 (7)	C6—C5—C51—C52	−78.4 (3)
C2—C21—C22—C271	14.6 (7)	C7—C6—C61—O6	133.4 (3)
C2—C21—C22—C23	151.5 (5)	C6—C61—N6—C62	175.6 (3)
C2—C21—C22—C231	−169.8 (5)		

Table 4

Hydrogen-bond geometry (\AA , $^\circ$) for polymorph (Ib).

$D-H\cdots A$	$D-H$	$H\cdots A$	$D\cdots A$	$D-H\cdots A$
N6—H6N \cdots O6 ⁱ	0.83 (3)	2.14 (3)	2.935 (3)	161 (3)
C27—H27 \cdots S1	0.93	2.63	3.257 (6)	125
C52—H52 \cdots O3 ⁱ	0.93	2.29	3.210 (4)	169

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

The N-bound H atoms were located in a difference density map and refined isotropically. All other H atoms were positioned geometrically and were treated as riding on their parent C atoms, with C—H distances of 0.93–0.98 \AA , and with $U_{\text{iso}}(\text{H}) = 1.5U_{\text{eq}}(\text{C})$ for

methyl atoms and $1.2U_{\text{eq}}(\text{C})$ for the other H atoms. In (Ib), atoms C23–C27 of the C22–C27 phenyl ring were found to be disordered. Refining the disordered model led to occupancy factors of 0.507 (4) and 0.493 (4), not significantly different from equal occupancy; in the final cycles, the occupancies of the disordered atoms were fixed at 0.5. The displacement parameters of the disordered atoms C23/C231, C24/C241, C25/C251, C26/C261 and C27/C271 were restrained to isotropic behaviour. The geometries of the disordered atoms were restrained, where distances were set to a target value of 1.39 \AA .

For both compounds, data collection: *SMART* (Bruker, 2001); cell refinement: *SAINT* (Bruker, 2001); data reduction: *SAINT*; program(s) used to solve structure: *SHELXS97* (Sheldrick, 1997); program(s) used to refine structure: *SHELXL97* (Sheldrick, 1997); molecular graphics: *SHELXTL/PC* (Sheldrick, 1990); software used to prepare material for publication: *SHELXL97*.

The authors thank Dr M. Meera Shetty for providing the compounds and Dr J. S. Yadav, Director, IICT, Hyderabad, for his kind encouragement.

Supplementary data for this paper are available from the IUCr electronic archives (Reference: GA3031). Services for accessing these data are described at the back of the journal.

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