1,3-Dimethyl-2-oxo-6-thioxo-1,2,3,6-tetrahydropurine (*S*-Theophylline)

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Abstract. $C_7H_8N_4OS$, $M_r = 196\cdot2$, orthorhombic, $Pbn2_1$, $a = 15\cdot614$ (3), $b = 8\cdot338$ (2), $c = 6\cdot570$ (2) Å, $U = 855\cdot4$ (4) Å^3, $Z = 4$, $D_x = 1\cdot52$ g cm^{-3}, λ(Mo $K\alpha$) $= 0\cdot71069$ Å, $\mu = 2\cdot9$ cm^{-1}, $F(000) = 408$, $T = 295$ K, $R = 0\cdot053$ for 653 observed reflections. The bond lengths and angles are normal for purine derivatives, with the five- and six-membered rings and S atom planar. The *S*-theophylline molecules, in contrast to the theophylline ones, are linked in chains by inter-molecular hydrogen bonding [N···O $2\cdot704$ (9) Å], but do not form the dimers found in the theophylline structure.

Introduction. The study of methylxanthine analogues (xanthine is 3,7-dihydro-1*H*-purine-2,6-dione) is attractive from both a theoretical and a practical point of view, in order to obtain methylxanthines whose therapeutic benefits have less limiting side effects. The replacement of oxygen with sulfur in the methyl-xanthine molecule drastically modifies the effects induced by the drugs on cardiac functionality (Fassina, Gaion, Caparotta & Carpenedo, 1985) and on lipolysis (Scotini, Carpenedo & Fassina, 1983).

The action of *S*-theophylline on guinea-pig cardiac atrial muscle differs from that of its natural analogue, theophylline. While theophylline increases the force of contraction, *S*-theophylline exerts a different action: it increases the cardiac contractility at low concentrations and diminishes this stimulating effect at high concentrations. The observed difference in action between theophylline and *S*-theophylline could be related to the physicochemical properties of the compounds.

While the crystal structure of theophylline (Sutor, 1958) and of several related compounds and, for example, its complexes with phenobarbital (Nakao, Fujii, Sakaki & Tomita, 1977), *p*-nitrophenol (Aoki, Ichikawa, Koinuma & Iitaka, 1978), copper chloride (Biagini Cingi, Manotti Lanfredi, Tiripicchio & Tiripicchio Camellini, 1979) and copper nitrate (Kindberg, Griffith, Amma & Jones, 1976) are known,

no up-to-date crystallographic information is available for *S*-theophylline.

The present crystal structure determination is part of our investigations on structure–activity relationships for drugs influencing the cardiac functionality.

Experimental. Compound crystallized from solution of methanol and dimethyl sulfoxide as white transparent needles of dimensions $0\cdot14 \times 0\cdot08 \times 0\cdot16$ mm; Philips PW 1100 diffractometer with monochromated Mo radiation; 25 reflections with $6 \leq \theta \leq 10°$ used for cell-dimension refinement; index ranges measured $h(0 \rightarrow 18)$, $k(0 \rightarrow 10)$, $l(0 \rightarrow 8)$; two reflections (121 and $0\bar{2}1$) measured after 180 min of X-ray exposure time showed no intensity variation; total reflections measured 1012, $\theta_{max} = 26°$; 653 reflections with $I > 3\sigma(I)$. Structure solved by direct methods (*SHELX*76; Sheldrick, 1976). Refinement of structure by full-matrix least-squares method with anisotropic thermal parameters for non-hydrogen atoms and overall isotropic thermal parameter ($U = 0\cdot07$ Å^2) for H introduced at calculated positions with idealized geometries and set to 'ride' on their bonded atoms; function minimized $\sum w(\Delta F)^2$ with $w = 1$; 124 refined parameters; goodness of fit $S = 0\cdot97$; final $(\Delta/\sigma)_{max}$ in final least-squares cycle $0\cdot09$; max. and min. $\Delta \rho$ $0\cdot4$ and $-0\cdot3$ e Å^{-3} in final difference synthesis; scattering factors from *International Tables for X-ray Crystallography* (1974). Computer programs: *SHELX*76 for structure determination and refinement (Sheldrick, 1976), *SHAKAL* for drawings (Keller, 1984) and *PARST* for molecular geometry calculations (Nardelli, 1983).*

Discussion. Final atomic parameters are in Table 1, and interatomic distances and angles in Table 2. Fig. 1 shows the molecular geometry with the atom numbering scheme used.

Table 1. *Atomic parameters: fractional coordinates* $(\times 10^4)$ *and* U_{eq} $(Å^2 \times 10^3)$ *with e.s.d.'s in parentheses*

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

	x	y	z	U_{eq}
S	6071 (1)	4811 (3)	2952†	59·2 (8)
O	7311 (4)	1785 (8)	8807 (10)	68 (2)
N(1)	6792 (4)	3246 (9)	6150 (11)	41 (2)
C(2)	7458 (6)	2609 (10)	7291 (13)	46 (3)
N(3)	8282 (4)	2982 (8)	6727 (12)	43 (2)
C(4)	8416 (4)	3833 (10)	4997 (12)	36 (3)
C(5)	7749 (5)	4375 (9)	3864 (14)	37 (2)
C(6)	6883 (5)	4125 (10)	4340 (14)	40 (2)
N(7)	8121 (4)	5174 (8)	2229 (10)	46 (2)
C(8)	8972 (4)	5037 (11)	2527 (14)	50 (3)
N(9)	9196 (4)	4273 (9)	4200 (13)	48 (2)
C(10)	5928 (5)	2904 (13)	6969 (17)	58 (3)
C(11)	9002 (6)	2397 (13)	7989 (20)	63 (3)

† Blocked for fixing the origin.

Table 2. *Bond lengths* (Å) *and bond angles* (°) *with standard deviations in parentheses*

S—C(6)	1·663 (9)	N(3)—C(4)	1·356 (11)
O—C(2)	1·231 (11)	C(4)—N(9)	1·376 (10)
N(1)—C(2)	1·388 (11)	N(9)—C(8)	1·318 (12)
N(1)—C(6)	1·404 (12)	C(8)—N(7)	1·348 (9)
N(1)—C(10)	1·480 (11)	N(7)—C(5)	1·391 (11)
N(3)—C(2)	1·374 (11)	C(5)—C(6)	1·403 (11)
N(3)—C(11)	1·480 (13)	C(4)—C(5)	1·358 (11)

S—C(6)—C(5)	124·1 (7)	C(11)—N(3)—C(4)	121·7 (7)
S—C(6)—N(1)	124·5 (6)	N(3)—C(4)—C(5)	121·0 (7)
C(5)—C(6)—N(1)	111·3 (8)	N(3)—C(4)—N(9)	126·5 (7)
C(6)—N(1)—C(2)	125·6 (7)	C(5)—C(4)—N(9)	112·4 (7)
C(6)—N(1)—C(10)	120·0 (7)	C(4)—C(5)—C(6)	124·6 (8)
C(10)—N(1)—C(2)	114·4 (7)	C(6)—C(5)—N(7)	130·2 (8)
O—C(2)—N(1)	120·7 (8)	C(4)—C(5)—N(7)	105·2 (7)
O—C(2)—N(3)	121·2 (8)	C(5)—N(7)—C(8)	105·0 (7)
N(1)—C(2)—N(3)	118·0 (8)	N(7)—C(8)—N(9)	115·1 (7)
C(2)—N(3)—C(11)	119·0 (8)	C(8)—N(9)—C(4)	102·2 (7)
C(2)—N(3)—C(4)	119·3 (7)		
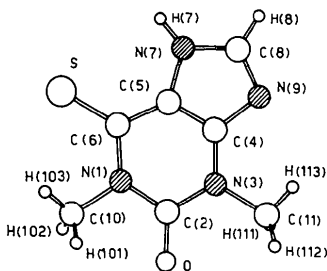
Bond lengths and angles are as expected for purine derivatives. The five- and six-membered condensed rings are approximately planar [the deviations from their weighted least-squares plane range from 0·019 (9) to —0·044 (9) Å]; the sulfur atom is coplanar [—0·023 (3) Å] as well as the C(11) (methyl) [—0·022 (12) Å] while C(10) (methyl) and O are slightly out of this plane [—0·080 (11), 0·094 (7) Å respectively].

The molecular packing shown in Fig. 2 differs from that of the theophylline monohydrate where the theophylline molecules are in dimeric arrangement by a pseudo symmetry centre (the space group is $P2_1$, nearly $P2_1/a$, and the structure has been refined by the approximation of the centrosymmetric space group) (Sutor, 1958) and are held together through intermolecular hydrogen bonding with the crystallized water molecules.

In the thiotheophylline derivative the oxygen attached to the C(6) atom is replaced by sulfur, which causes a chain arrangement of the compound, which is not hydrated in this case. As shown in Fig. 2, the interaction between the molecules in each chain is determined by hydrogen bonding between N(7) and O'(1·5—x, 0·5+y, z—1), N(7)···O' 2·704 (9) Å, N(7)—H(7)···O' 160 (6)°. The presence of sulfur instead of oxygen hinders dimer formation, but in some sense favours the packing of the molecules in chains. This stabilizes the solid-state structure in the absence of the crystallization water molecules that in the case of theophylline play a stabilizing role with the formation of hydrogen bonds between the dimeric units.

The S···S separation between adjacent chains is 4·699 (4) Å.

The different pharmacological actions of theophylline and S-theophylline could be related to the difference in the crystal packing mode, if maintained in solution, and consequently to the different permeation rate across the biological membrane.
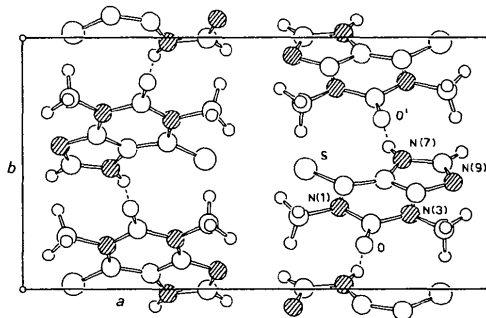

Fig. 1. View of the molecule parallel to the imidazole ring.

Fig. 2. Cell contents viewed down c.

References

AOKI, K., ICHIKAWA, T., KOINUMA, Y. & IITAKA, Y. (1978). *Acta Cryst.* B34, 2333–2336.

BIAGINI CINGI, M., MANOTTI LANFREDI, A. M., TIRIPICCHIO, A. & TIRIPICCHIO CAMELLINI, M. (1979). *Transition Met. Chem.* 4, 221–224.

FASSINA, G., GAION, R. M., CAPAROTTA, L. & CARPENEDO, L. (1985). *Arch. Pharmacol.* 330, 226.

International Tables for X-ray Crystallography (1974). Vol. IV. Birmingham: Kynoch Press. (Present distributor D. Reidel, Dordrecht.)

KELLER, F. (1984). *SHAKAL.* Univ. of Freiburg, Federal Republic of Germany.

KINDBERG, B. L., GRIFFITH, E. A., AMMA, E. L. & JONES, E. R. (1976). *Cryst. Struct. Commun.* 5, 533–538.

NAKAO, S., FUJII, S., SAKAKI, T. & TOMITA, K. (1977). *Acta Cryst.* B33, 1373–1378.

NARDELLI, M. (1983). *Comput. Chem.* 7, 95–98.

SCOTINI, E., CARPENEDO, F. & FASSINA, G. (1983). *Pharmacol. Res. Commun.* 15, 131–143.

SHELDRICK, G. M. (1976). *SHELX76.* Program for crystal structure determination. Univ. of Cambridge, England.

SUTOR, D. J. (1958). *Acta Cryst.* 11, 83–87.

Structure of 2-(1,5-Dimethyl-4-hexenyl)-3-hydroxy-5-methyl-1,4-benzoquinone (Perezone), a Sesquiterpene*

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Abstract. $C_{15}H_{20}O_3$, $M_r = 248\cdot3$, monoclinic, $P2_1$, $a = 6\cdot662$ (3), $b = 7\cdot343$ (3), $c = 14\cdot537$ (6) Å, $\beta = 98\cdot20$ (4)°, $V = 703\cdot9$ (1) Å^3, $Z = 2$, $D_x = 1\cdot17$ Mg m^{-3}, $\lambda(\text{Mo }K\alpha) = 0\cdot7107$ Å, $\mu = 0\cdot075$ mm^{-1}, $F(000) = 268$, $T = 293$ K. Final $R = 0\cdot052$ for 796 observed reflections. The structural features determined from chemical and spectroscopic studies are confirmed and extended. The quinone ring is planar and shows normal geometry. The side chain at C(3) adopts an extended form and is oriented out of the plane of the quinone ring. The angle between the plane of the quinone ring and the side chain is $102\cdot6$ (6)°. The molecules in the crystal are held together by hydrogen bonds and van der Waals interactions.

Introduction. Perezone (1) is a sesquiterpene compound which was isolated from the roots of a plant, *Perezia adnata*, a member of the Compositae family found in

Mexico. This compound exerts very marked physiological action, having purgative properties for which it is much used in Mexico. The chemical and spectroscopic studies led to the proposal of the chemical structure (1) from four different laboratories (Archer & Thomson, 1965; Walls, Salmón, Padilla, Joseph-Nathan & Romo, 1965; Wagner, Moss, Brooker, Heeschen, Potts & Dilling, 1965; Bates, Paknikar & Thalacker, 1965) and this was confirmed by synthesis (Cortés, Salmón & Walls, 1965).

(1)
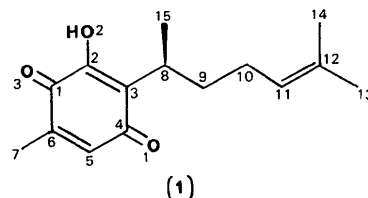
The X-ray crystallographic structural determination of (1) was undertaken in order to establish the crystal structure and the stereochemistry of this compound.