Del Bel Belluz, P., Cordes, A. W., Kristof, E. M., Kristof, P. V., Liblong, S. W. & Oakley, R. T. (1989). *J. Am. Chem. Soc.* **111**, 9276–9279.
Ibers, J. A. & Hamilton, W. C. (1964). *Acta Cryst.* **17**, 781–782.
Johnson, C. K. (1976). *ORTEP*II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, USA.
Molecular Structure Corporation (1988). *MSC/AFC Diffractometer Control Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
Molecular Structure Corporation (1994). *TEXSAN. Single Crystal Structure Analysis Software*. MSC, 3200 Research Forest Drive, The Woodlands, TX 77381, USA.
North, A. C. T., Phillips, D. C. & Mathews, F. S. (1968). *Acta Cryst.* A**24**, 351–359.
Oakley, R. T. (1993). *Can. J. Chem.* **71**, 1775–1784.
Zachariasen, W. H. (1968). *Acta Cryst.* A**24**, 212–216.

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8-Amino-7-(2-hydroxy-3-morpholinopropyl)theophylline

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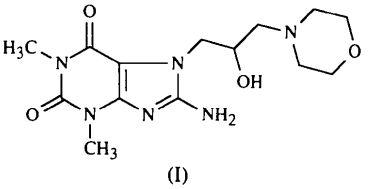
Abstract

The purine fused-ring skeleton in the title compound, 8-amino-7-(2-hydroxy-3-morpholinopropyl)-1,3-dimethyl-3,7-dihydro-1*H*-purine-2,6-dione, $C_{14}H_{22}N_6O_4$, is planar, while the morpholine ring adopts a chair conformation. Statistical disorder occurs within the hydroxy group. The structure is stabilized by a network of intermolecular hydrogen bonds and the conformation of the 7-amino-hydroxyalkyl substituent is determined by an O—H···N intramolecular hydrogen bond.

Comment

Pharmacological investigation of a series of 7,8-disubstituted derivatives of theophylline revealed that some of these compounds exhibited potent antihypertensive and vasodilator activity (Łucka-Sobstel *et al.*, 1985; Gorczyca, Pawłowski, Mrozikiewicz, Kozłowska & Wasik, 1986; Olejnik *et al.*, 1989). Of a number of compounds studied, the title structure, (I), was chosen for more detailed pharmacological screening (Pawłowski, Gorczyca, Bobkiewicz-Kozłowska, Chodera & Mrozikiewicz, 1991). Circulatory effects, mainly antihypertensive activity, the beneficial effect on cerebral blood-flow autoregulation (Kozłowska *et al.*, 1989) and low toxicity in comparison with its mother compound theophylline (aminophylline) suggest the need to test the clinical effectiveness of (I) in order to obtain a new therapeutic agent.



(I)

We report here the results of the X-ray structure determination of (I) as part of a larger structural and pharmacological study on 7,8-disubstituted theophylline derivatives. The complete crystal structure analysis was expected to yield information concerning the effects of substituents on receptor affinities of compound (I).

Bond lengths and angles in the theophylline skeleton do not differ significantly from those reported for theophylline (Sutor, 1958) and its 7,8-disubstituted derivatives (Karolak-Wojciechowska & Pawłowski, 1990; Karczmarzyk, Karolak-Wojciechowska & Pawłowski, 1991). In the purine fused-ring system the six-membered ring is planar to within 0.012 (3) Å and the five-membered ring is planar to within 0.004 (3) Å. These two rings are inclined at an angle of 0.9 (1)° with respect to each other. The length of the N6—C6 bond and the sum of the valence angles around the N6 atom (358.2°) show that this atom is sp^2 hybridized and that the amino group is conjugated with the π system of the imidazole ring.

The morpholine ring adopts a chair conformation with puckering parameters (Cremer & Pople, 1975) of Q = 0.5593 Å and θ = 178.4°. The most noteworthy feature is the geometry of the pyramidal N13 ring atom. The C12—N13—C18 angle is significantly larger than the C12—N13—C14 and C14—N13—C18 angles. The opening of this angle indicates a distorted tetrahedral configuration around the N13 atom, probably caused by steric effects. We were particularly interested in the conformation of the aminohydroxyalkyl substituent in the 7-position of the molecule. The torsion angles C6—N5—C10—C11 = −77.0 (3), N5—C10—C11—C12 = −73.2 (3), C10—C11—C12—N13 = −179.7 (3) and C11—C12—N13—C14 = 160.1 (3)° indicate a *gauche*–

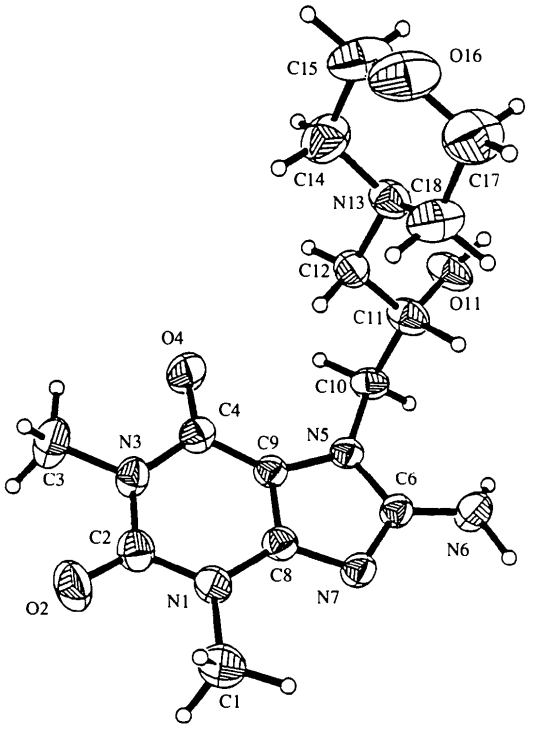


Fig. 1. The molecular conformation and atomic numbering of the title compound. Displacement ellipsoids are plotted at the 50% probability level.

gauche–trans–gauche conformation of the 2-hydroxypropyl side chain. The conformation of the hydroxy group with respect to the N5—C10 and C12—N13 bonds is *gauche–gauche*, with torsion angles N5—C10—C11—O11 = 159.6 (2) and O11—C11—C12—N13 = −56.7 (4)°. The major conformation-determining feature for the substituent at the 7-position of the molecule is the presence of an O11—H···N13 intramolecular hydrogen bond.

The molecular packing in the crystal is determined by the presence of a network of hydrogen bonds. The amino group acts as a donor, atom N7 from the imidazole ring and the carbonyl O4 atom act as acceptors, while the hydroxy group exhibits both donor and acceptor capabilities. Hydrogen-bonded molecules form layers parallel to the (100) plane. Neighbouring layers are held together by van der Waals forces alone. The hydrogen-bond geometry is given in Table 3.

Experimental

8-Amino-7-(2-hydroxy-3-morpholinopropyl)theophylline was prepared according to the method of Pawłowski *et al.* (1991). Crystals suitable for X-ray diffraction analysis, occurring as the racemates of two enantiomers, were grown by slow evaporation of an ethanol solution.

Crystal data

$C_{14}H_{22}N_6O_4$
M_r = 338.37
Monoclinic
$C2/c$
a = 26.114 (5) Å
b = 9.859 (2) Å
c = 13.273 (3) Å
β = 108.48 (3)°
V = 3241 (1) Å^3
Z = 8
D_x = 1.387 Mg m^{-3}
Cu $K\alpha$ radiation
λ = 1.54184 Å
Cell parameters from 25 reflections
θ = 10–50°
μ = 0.776 mm^{-1}
T = 293 K
Plate
0.25 × 0.20 × 0.10 mm
Colourless

Data collection

Kuma KM-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
7745 measured reflections
3182 independent reflections
2795 observed reflections [$F > 4\sigma(F)$]
R_{int} = 0.0078
θ_{max} = 82°
$h = -30 \rightarrow 30$
$k = 0 \rightarrow 12$
$l = 0 \rightarrow 16$
2 standard reflections monitored every 100 reflections
intensity decay: none

Refinement

Refinement on F
R = 0.0667
wR = 0.0667
S = 3.43
2795 reflections
243 parameters
Unit weights applied
$(\Delta/\sigma)_{max}$ = 0.059
$\Delta\rho_{max}$ = 0.27 e Å^{-3}
$\Delta\rho_{min}$ = −0.38 e Å^{-3}
Atomic scattering factors from *SHELX*76 (Sheldrick, 1976)

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

U_{iso} for O11*P* and O12*P*; $U_{eq} = (1/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$ for others.

	x	y	z	U_{eq}/U_{iso}
N1	0.4151 (1)	−0.0544 (2)	0.1790 (2)	0.0382 (4)
N3	0.3820 (1)	0.1136 (2)	0.0484 (2)	0.0397 (4)
N5	0.4517 (1)	0.2530 (2)	0.3156 (2)	0.0326 (4)
N6	0.4974 (1)	0.1910 (3)	0.4931 (2)	0.0456 (6)
N7	0.4609 (1)	0.0310 (2)	0.3561 (2)	0.0362 (4)
N13	0.3170 (1)	0.4972 (3)	0.3519 (2)	0.0459 (7)
O2	0.3698 (1)	−0.1111 (2)	0.0085 (2)	0.0566 (6)
O4	0.3934 (1)	0.3415 (2)	0.0860 (2)	0.0518 (6)
O16	0.2119 (1)	0.4969 (3)	0.3717 (3)	0.0829 (10)
C1	0.4198 (2)	−0.1974 (3)	0.2106 (3)	0.0616 (11)
C2	0.3878 (1)	−0.0238 (3)	0.0751 (2)	0.0413 (8)
C3	0.3510 (1)	0.1430 (4)	−0.0625 (2)	0.0571 (8)
C4	0.4006 (1)	0.2226 (3)	0.1187 (2)	0.0367 (6)
C6	0.4711 (1)	0.1594 (3)	0.3929 (2)	0.0332 (4)
C8	0.4335 (1)	0.0472 (3)	0.2519 (2)	0.0328 (4)
C9	0.4264 (1)	0.1810 (3)	0.2220 (2)	0.0328 (4)
C10	0.4546 (1)	0.4002 (3)	0.3309 (2)	0.0364 (6)
C11	0.4129 (1)	0.4501 (3)	0.3798 (3)	0.0453 (3)
C14	0.2695 (1)	0.5356 (4)	0.2653 (3)	0.0657 (10)
C15	0.2264 (2)	0.5899 (4)	0.3057 (4)	0.0781 (12)
C17	0.2578 (2)	0.4617 (5)	0.4589 (4)	0.0832 (12)
C18	0.3018 (2)	0.4021 (4)	0.4198 (3)	0.0691 (10)
O11†	0.4304 (1)	0.5761 (2)	0.4246 (2)	0.0518 (6)
C12†	0.3574 (1)	0.4483 (4)	0.3050 (3)	0.0408 (8)
O11*P*‡	0.4315 (6)	0.4563 (18)	0.4819 (13)	0.059 (4)
C12*P*‡	0.3604 (9)	0.389 (2)	0.3499 (18)	0.045 (5)

† Site occupancy factor of 0.85.
‡ Site occupancy factor of 0.15.

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

N1—C1	1.465 (4)	N13—C12*P*	1.57 (2)
N1—C2	1.369 (3)	O2—C2	1.217 (3)
N1—C8	1.370 (3)	O4—C4	1.243 (3)
N3—C2	1.396 (4)	O16—C15	1.401 (5)
N3—C3	1.467 (3)	O16—C17	1.418 (5)
N3—C4	1.405 (3)	C4—C9	1.384 (4)
N5—C6	1.353 (3)	C8—C9	1.373 (4)
N5—C9	1.401 (3)	C10—C11	1.517 (4)
N5—C10	1.464 (3)	C11—O11	1.390 (3)
N6—C6	1.326 (3)	C11—C12	1.473 (4)
N7—C6	1.353 (3)	C11—O11*P*	1.289 (16)
N7—C8	1.350 (3)	C11—C12*P*	1.44 (2)
N13—C14	1.449 (4)	C14—C15	1.491 (5)
N13—C18	1.441 (4)	C17—C18	1.521 (5)
N13—C12	1.467 (4)		
C1—N1—C2	118.0 (2)	N5—C6—N7	112.4 (2)
C1—N1—C8	121.5 (2)	N6—C6—N7	124.2 (2)
C2—N1—C8	120.3 (2)	N1—C8—N7	126.2 (2)
C2—N3—C3	115.3 (2)	N1—C8—C9	120.9 (2)
C2—N3—C4	125.9 (2)	N7—C8—C9	112.9 (2)
C3—N3—C4	118.7 (2)	N5—C9—C4	132.3 (2)
C6—N5—C9	106.6 (2)	N5—C9—C8	104.3 (2)
C6—N5—C10	125.4 (2)	C4—C9—C8	123.4 (2)
C9—N5—C10	127.9 (2)	N5—C10—C11	111.7 (2)
C6—N7—C8	103.8 (2)	C10—C11—O11	106.8 (2)
C14—N13—C18	109.3 (3)	C10—C11—C12	113.2 (3)
C14—N13—C12	107.4 (3)	C10—C11—O11*P*	112.4 (7)
C14—N13—C12*P*	127.4 (8)	C10—C11—C12*P*	119.8 (9)
C18—N13—C12	115.5 (3)	O11—C11—C12	114.8 (3)
C18—N13—C12*P*	84.9 (9)	C12—C11—O11*P*	132.3 (8)
C15—O16—C17	110.2 (3)	O11*P*—C11—C12*P*	108.7 (12)
N1—C2—N3	116.7 (2)	N13—C14—C15	111.2 (3)
N1—C2—O2	122.2 (3)	O16—C15—C14	112.0 (3)
N3—C2—O2	121.1 (3)	O16—C17—C18	110.4 (3)
N3—C4—O4	120.5 (2)	N13—C18—C17	110.5 (3)
N3—C4—C9	112.8 (2)	N13—C12—C11	113.3 (3)
O4—C4—C9	126.7 (3)	N13—C12*P*—C11	109.9 (14)
N5—C6—N6	123.4 (2)		

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

D—H···*A*	*D*—H	H···*A*	*D*···*A*	*D*—H···*A*
N6—H61···O11^{i}	0.74 (4)	2.26 (3)	2.953 (3)	156 (4)
N6—H62···N7^{ii}	0.99 (3)	1.94 (3)	2.933 (3)	176 (3)
O11—HO11···O4^{iii}	0.92 (4)	1.86 (4)	2.737 (4)	160 (3)

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

The systematic absences showed the space group to be *C*2/*c* or *Cc*. The normalized structure-factor statistics favoured the centrosymmetric space group *C*2/*c* and subsequent analysis confirmed this. The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1985) and refined by full-matrix least squares with *SHELX*76 (Sheldrick, 1976). All H atoms, except those of the amino and hydroxy groups, which were located from a $\Delta\rho$ map, were placed in calculated positions and refined using a riding model with isotropic displacement parameters taken as 1.5 times those of the respective parent C atoms. During the course of the refinement, two peaks were found adjacent to the —CH(OH)CH$_2$— moiety with intensities of 1.19 and 0.58 e Å^{-3}. Based on their locations, one was assigned to atom O11*P* and the other to atom C12*P*. Occupancy factors were allowed to vary in the subsequent cycles of refinement and were fixed at 0.85 for atoms O11 and C12, and at 0.15 for atoms O11*P* and C12*P* in the final cycles of refinement. Atoms O11*P* and C12*P* were refined with isotropic temperature factors. The molecular plot was prepared with *SHELXTL-Plus XP* (Sheldrick, 1989). The geometrical calculations and material for publication were produced using *PARST* (Nardelli, 1983) and *CSU*88 (Vickovič, 1988)

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AS1159). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

References

Cremer, D. & Pople, J. A. (1975). *J. Am. Chem. Soc.* **97**, 1354–1358.

Gorczyca, M., Pawłowski, M., Mrozikiewicz, A., Kozłowska, T. & Wasik, A. (1986). *Pol. J. Pharmacol. Pharm.* **38**, 85–90.

Karczmarzyk, Z., Karolak-Wojciechowska, J. & Pawłowski, M. (1991). *Acta Cryst.* C**47**, 1902–1904.

Karolak-Wojciechowska, J. & Pawłowski, M. (1990). *J. Crystallogr. Spectrosc. Res.* **20**, 477–482.

Kozłowska, T., Olejnik, A., Krawczak, J., Chodera, A., Barry, D. & Pedersen, E. (1989). *Pol. J. Pharmacol. Pharm.* **41**, 611–618.

Łucka-Sobstel, B., Pawłowski, M., Gorczyca, M., Olejnik, A., Kozłowska, T. & Chodera, A. (1985). *Mem. Pharm.* **166**, 35–42.

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

Olejnik, A., Kozłowska, T., Beutler, A., Krawczak, J., Chodera, A., Pawłowski, M. & Gorczyca, M. (1989). *Mem. Pharm.* **170**, 77–85.

Pawłowski, M., Gorczyca, M., Bobkiewicz-Kozłowska, T., Chodera, A. & Mrozikiewicz, A. (1991). Polish Patent applications P-291306 and P-291307.

Sheldrick, G. M. (1976). *SHELX*76. *Program for Crystal Structure Determination.* Univ. of Cambridge, England.

Sheldrick, G. M. (1985). *SHELXS*86. *Program for the Solution of Crystal Structures.* Univ. of Göttingen, Germany.

Sheldrick, G. M. (1989). *SHELXTL-Plus.* Release 4.0. Siemens Analytical X-ray Instruments Inc., Madison, Wisconsin, USA.

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

Vickovič, J. (1988). *CSU*88. *Crystal Structure Utility. Program for Geometrical Calculations.* Univ. of Zagreb, Croatia.

Acta Cryst. (1995). C**51**, 2123–2125

3,3-Dibenzylpentane-2,4-dione, $C_{19}H_{20}O_2$

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Abstract

The notable feature of the title compound is the non-planarity of the pentane-2,4-dione moiety. This fragment of the molecule adopts a significantly distorted *S* conformation with a dihedral angle of 62.1 (2)° between the planes through C1—C2(=O1)—C3 and C3—C4(=O2)—C5. The molecular packing involves C—H···O close contacts.