Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, complete geometry and least-squares-planes data, and packing diagrams viewed down the *b* and *c* axes have been deposited with the IUCr (Reference: TA1027). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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7-[3-(Dibenzylamino)-2-hydroxypropyl]-8-(furfurylamino)theophylline

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Abstract

The theophylline moiety of the title compound, 7-[3-(dibenzylamino)-2-hydroxypropyl]-8-(furfurylamino)-3,7-dihydro-1,3-dimethyl-1*H*-purine-2,6-dione, $C_{29}H_{32}N_6O_4$, is planar. The conformation of the 7-aminohydroxy-alkyl substituent may be influenced by an O—H···N intramolecular hydrogen bond and the structure is stabilized by an N—H···O intermolecular bond.

Comment

As part of our studies of the structures and pharmacological properties of 7,8-disubstituted derivatives of theophylline (Karolak-Wojciechowska & Pawłowski, 1990; Karczmarzyk, Karolak-Wojciechowska & Pawłowski, 1991, 1995), we report here the results of an X-ray structure determination of the title compound, (I), which shows potent antihypertensive and vasodilating activity. A tertiary N atom with two benzyl groups present in the substituent at the 7 position may be responsible for this pharmacological effect (Olejnik *et al.*, 1989).

(I)
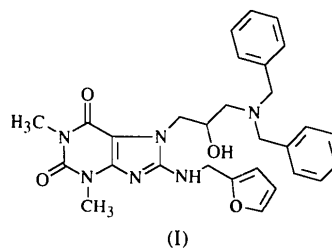
Both rings of the theophylline moiety are planar: to within 0.028 (2) Å for the six-membered ring and 0.010 (2) Å for the five-membered ring. They are inclined at 1.3 (1)° with respect to each other. The amino group of the 8-furfurylamine substituent is conjugated with the π-electron system of the imidazole ring [N8—C8 = 1.347 (3) Å] and the sum of valence angles around C8 is 356 (3)°.

One particular reason for the present study was the determination of the conformation of the amino-hydroxyalkyl substituent at the 7 position of the molecule. The conformation of the 2-hydroxyamino-propyl side chain is *gauche–gauche–trans–gauche*. The orientation of the hydroxy group with respect to the N7—C7 and C12—N13 bonds is *trans–gauche*. The conformation of the substituent is stabilized by an O11—H11O···N13 intramolecular hydrogen bond [O11···N13 2.822 (3), H11O···N13 2.29 (4) Å and O11—H11O···N13 129 (5)°]; this type of hydrogen bond has also been observed in a similar 7,8-disubstituted derivative of theophylline (Karczmarzyk, Karolak-Wojciechowska & Pawłowski, 1995). The phenyl rings are planar; their least-squares planes are inclined by 53.4 (1)° with respect to each other and by 78.7 (1) and 28.0 (1)° with respect to the plane of the theophylline moiety. The position of the benzyl substituents with respect to the C12—N13 bond is given by the torsion angles C12—N13—C21—C22 = 166.2 (2) and C12—N13—C31—C32 = −74.7 (3)°.

The furfurylamino group in position 8 possesses a *trans–gauche–gauche* conformation. The geometry of the furan ring does not show any unusual features (Galešić, Vlahov & Galešić, 1987).
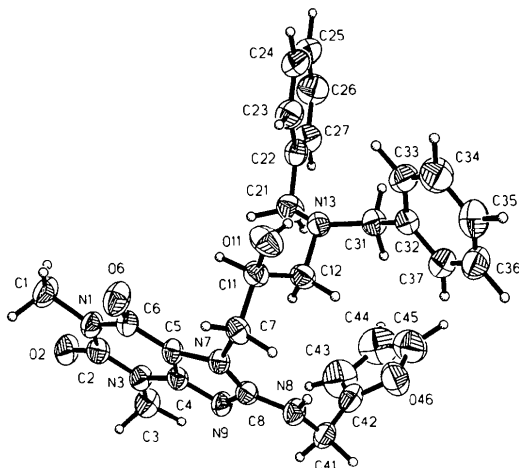
Fig. 1. A view of the molecule with the atomic labelling. Non-H atoms are represented by displacement ellipsoids of 50% probability.

The molecules in the crystal are joined in chains parallel to **a** by an N8—H81···O2(1 + x, y, z) intermolecular hydrogen bond: N8···O2 2.926(3), H81···O2 2.19(4) Å and N8—H81···O2 154(3)°. Neighbouring chains are held together by van der Waals forces only.

Experimental

The title compound was prepared according to the method described by Pawlowski, Gorczyca & Łucka-Sobstel (1985). Racemic crystals suitable for X-ray diffraction were grown by slow evaporation of an ethanol solution.

Crystal data

$C_{29}H_{32}N_6O_4$	Cu $K\alpha$ radiation
$M_r = 528.61$	$\lambda = 1.54184$ Å
Triclinic	Cell parameters from 25
$P\bar{1}$	reflections
$a = 9.432(1)$ Å	$\theta = 10–50°$
$b = 12.080(2)$ Å	$\mu = 0.649$ mm^{-1}
$c = 12.542(2)$ Å	$T = 293$ K
$\alpha = 97.98(1)°$	Plate
$\beta = 96.42(1)°$	$0.40 \times 0.30 \times 0.20$ mm
$\gamma = 107.87(1)°$	Colourless
$V = 1328.6(4)$ Å^3	
$Z = 2$	
$D_x = 1.321$ Mg m^{-3}	

Data collection

Kuma KM-4 diffractometer	$\theta_{max} = 82°$
$\omega/2\theta$ scans	$h = -11 \rightarrow 11$
Absorption correction:	$k = -14 \rightarrow 14$
none	$l = 0 \rightarrow 16$
5740 measured reflections	2 standard reflections
4718 independent reflections	monitored every 100
3972 observed reflections	reflections
[$F > 4\sigma(F)$]	intensity decay: none
$R_{int} = 0.0253$	

Refinement

Refinement on F	$\Delta\rho_{max} = 0.31$ e Å^{-3}
$R = 0.0563$	$\Delta\rho_{min} = -0.19$ e Å^{-3}
$wR = 0.0723$	Extinction correction:
$S = 1.49$	$F_c{}^* = F_c(1 - gF_c^2/\sin\theta)$
3972 reflections	Extinction coefficient:
367 parameters	$g = 11.5(3) \times 10^{-7}$
$w = 4.5734[\sigma^2(F_o)$	Atomic scattering fac-
$\quad + 0.00049F_o^2]$	tors from *SHELX76*
$(\Delta/\sigma)_{max} = 0.004$	(Sheldrick, 1976)

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

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

	x	y	z	U_{eq}/U_{iso}
N1	-0.0040(2)	0.4827(2)	0.3355(2)	0.0440(4)
N3	-0.0099(2)	0.3275(2)	0.4318(2)	0.0431(4)
N7	0.3612(2)	0.4249(2)	0.3765(2)	0.0369(4)
N8	0.4828(2)	0.3040(2)	0.4573(2)	0.0437(4)
N9	0.2258(2)	0.2857(2)	0.4624(2)	0.0400(4)
N13	0.4064(2)	0.2364(2)	0.0646(2)	0.0436(4)
O2	-0.2181(2)	0.3801(2)	0.3935(2)	0.0571(4)
O6	0.2126(2)	0.5930(2)	0.2813(2)	0.0598(6)
O46	0.5377(3)	0.0681(2)	0.3593(2)	0.0746(8)
C1	-0.0915(3)	0.5479(3)	0.2817(3)	0.0597(8)
C2	-0.0851(3)	0.3953(3)	0.3867(2)	0.0447(6)
C3	-0.0930(3)	0.2333(3)	0.4855(3)	0.0532(7)
C4	0.1393(2)	0.3463(2)	0.4216(2)	0.0366(4)
C5	0.2137(2)	0.4306(2)	0.3679(2)	0.0377(4)
C6	0.1506(3)	0.5099(2)	0.3250(2)	0.0425(4)
C7	0.4728(3)	0.4810(2)	0.3117(2)	0.0407(4)
C8	0.3600(2)	0.3356(2)	0.4318(2)	0.0370(4)
C11	0.4311(3)	0.4162(2)	0.1929(2)	0.0451(4)
C12	0.4397(3)	0.2919(2)	0.1802(2)	0.0458(4)
C21	0.2433(3)	0.1766(3)	0.0281(2)	0.0527(7)
C22	0.2022(3)	0.1446(2)	-0.0946(2)	0.0464(7)
C23	0.2553(4)	0.2270(3)	-0.1607(3)	0.0551(8)
C24	0.2187(4)	0.1972(3)	-0.2724(3)	0.0616(8)
C25	0.1280(4)	0.0856(4)	-0.3212(3)	0.0699(10)
C26	0.0711(4)	0.0022(4)	-0.2572(3)	0.0745(8)
C27	0.1090(4)	0.0328(3)	-0.1441(3)	0.0594(8)
C31	0.4892(3)	0.1522(3)	0.0434(3)	0.0508(8)
C32	0.6536(3)	0.2164(3)	0.0447(2)	0.0472(7)
C33	0.6977(4)	0.2885(3)	-0.0314(3)	0.0589(8)
C34	0.8470(4)	0.3469(3)	-0.0325(3)	0.0731(11)
C35	0.9568(4)	0.3357(3)	0.0447(3)	0.0700(10)
C36	0.9159(4)	0.2668(3)	0.1215(3)	0.0629(8)
C37	0.7651(3)	0.2072(3)	0.1215(3)	0.0562(8)
C41	0.4715(3)	0.1948(3)	0.4987(2)	0.0498(7)
C42	0.4279(3)	0.0883(3)	0.4130(3)	0.0526(7)
C43	0.2977(5)	0.0044(4)	0.3737(4)	0.0888(13)
C44	0.3272(7)	-0.0760(4)	0.2899(5)	0.1015(15)
C45	0.4697(6)	-0.0348(4)	0.2841(4)	0.0882(14)
O11†	0.5267(3)	0.4843(2)	0.1319(2)	0.0626(8)
O11'†	0.3333(19)	0.4435(14)	0.1387(14)	0.065(5)

† Occupancies of O11 and O11' are 0.84(1) and 0.16(1), respectively.

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

N1—C1	1.476(3)	N9—C4	1.357(3)
N1—C2	1.384(3)	N9—C8	1.348(3)
N1—C6	1.418(3)	O2—C2	1.225(3)
N3—C2	1.373(3)	O6—C6	1.231(3)
N3—C3	1.466(3)	C4—C5	1.356(3)
N3—C4	1.379(3)	C5—C6	1.408(3)
N7—C5	1.407(3)	C11—O11	1.397(3)
N7—C8	1.358(3)	C11—O11'	1.237(18)
C1—N1—C2	115.6(2)	N9—C4—C5	113.5(2)
C1—N1—C6	118.0(2)	N7—C5—C4	104.8(2)
C2—N1—C6	126.3(2)	N7—C5—C6	131.1(2)
C2—N3—C3	118.8(2)	C4—C5—C6	123.8(2)

C2—N3—C4	119.5 (2)	N1—C6—O6	120.6 (2)
C3—N3—C4	121.7 (2)	N1—C6—C5	111.4 (2)
C5—N7—C7	124.3 (2)	O6—C6—C5	128.0 (2)
C5—N7—C8	105.4 (2)	N7—C8—N8	123.1 (2)
C7—N7—C8	128.1 (2)	N7—C8—N9	113.3 (2)
C4—N9—C8	102.9 (2)	N8—C8—N9	123.6 (2)
N1—C2—N3	117.4 (2)	C7—C11—O11	108.0 (2)
N1—C2—O2	121.4 (2)	C7—C11—O11'	113.2 (8)
N3—C2—O2	121.1 (3)	C12—C11—O11	111.1 (2)
N3—C4—N9	125.2 (2)	C12—C11—O11'	123.6 (8)
N3—C4—C5	121.3 (2)		
C8—N7—C7—C11	89.3 (3)	O11—C11—C12—N13	−55.6 (3)
N7—C7—C11—C12	−66.3 (3)	N7—C8—N8—C41	−168.7 (2)
C7—C11—C12—N13	−177.1 (2)	C8—N8—C41—C42	83.0 (3)
C11—C12—N13—C21	−87.7 (3)	N8—C41—C42—O46	80.1 (4)
N7—C7—C11—O11	170.5 (2)		

All H atoms (except those of the amino groups, the hydroxy groups and those bonded to C11, which were located from $\Delta\rho$ syntheses) were located in calculated positions and refined using a riding model with isotropic displacement parameters taken as $1.5U_{eq}$ of their respective parent C atoms. During the course of the refinement, a peak was found in the vicinity of the hydroxy group with intensity $+1.31$ e Å^{-3}. The hydroxy O atom was split between the positions O11 and O11'. Occupancy factors were allowed to vary in the subsequent cycles of refinement and were fixed at 0.84 (1) for O11 and 0.16 (1) for O11' in the final cycles. O11' was refined with an isotropic displacement parameter; all other non-H atoms were refined with anisotropic displacement parameters.

The structure was solved by direct methods using *SHELXS*86 (Sheldrick, 1990) and refined by full-matrix least squares using *SHELX*76 (Sheldrick, 1976). Molecular graphics were prepared using *XP* (Sheldrick, 1989). *PARST* (Nardelli, 1983) and *CSU*88 (Vicković, 1988) were used for geometrical calculations and to prepare material for publication.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: AB1278). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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8-Benzylamino-7-{2-hydroxy-3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl}theophylline

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Abstract

The molecules of the title compound, 8-benzylamino-3,7-dihydro-7-{2-hydroxy-3-[4-(2-hydroxyethyl)-1-piperazinyl]propyl}-1,3-dimethyl-1*H*-purine-2,6-dione, $C_{23}H_{33}N_7O_4$, have a typical geometry: the fused rings of the purine system are planar and are inclined with respect to each other at an angle of 0.6 (1)°. The amino-hydroxyalkyl group in the 7 position of the theophylline has a *gauche–trans–gauche–gauche* conformation, while the benzylamine group in the 8 position has a *trans–gauche–trans* conformation. The piperazine ring adopts a chair conformation with puckering parameters $Q = 0.592$ (3) Å and $\theta = 178.0$ (3)° [Cremer & Pople (1975). *J. Am. Chem. Soc.* 97, 1354–1358]. The amino group of the 8-benzylamine substituent is conjugated with the π-electron system of the imidazole ring [N8—C8 = 1.343 (3) Å] and the sum of the valence angles around C8 is 359.8°. Molecules are joined by a network of hydrogen bonds: N8$\cdots$O2($-1 + x$, y, z) 2.824 (4), O11$\cdots$O20($x, y, 1 + z$) 2.781 (4) and O20$\cdots$N16 ($1 - x, -y, -1 - z$) 2.852 (3) Å.

Comment

Methylxanthines (caffeine, theophylline and theobromine) are well known as compounds of significant biological activity. Since the addition of selected sub-