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.

The crystallographic studies were supported by grant No. 3 0302 91 01 from the Polish State Committee for Scientific Research.

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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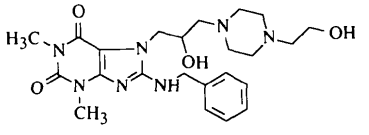
Abstract

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 θ = 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···O2($-1+x, y, z$) 2.824 (4), O11···O20($x, y, 1+z$) 2.781 (4) and O20···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-

stituents, in the 7 and 8 positions of theophylline, for example, can modify the pharmacological profile of the parent compound, methylxanthines constitute interesting subjects for the search for a correlation between structure and activity. This prompted us to synthesize a series of 7,8-disubstituted derivatives of theophylline, pharmacological investigation of which showed that some have antihypertensive and vasodilatory activity (Łucka-Sobstel *et al.*, 1985; Gorczyca, Pawłowski, Mrozikiewicz, Kozłowska & Wasik, 1986; Olejnik *et al.*, 1989). As structure–activity correlations can be based on structural and electronic parameters derived from a geometrical description of the molecule, the three-dimensional structures and conformations of all molecules investigated have to be known. The crystal structure of the title compound, (I), is part of a larger X-ray study of 7,8-disubstituted theophylline derivatives (Karolak-Wojciechowska & Pawłowski, 1990; Karczmarzyk, Karolak-Wojciechowska & Pawłowski, 1991, 1995).



(I)

The principal aims of this structure determination of the pharmacologically inactive derivative (I) were to establish the conformation and mutual orientation of the substituents, the changes in the geometrical parameters of the molecular skeleton in comparison to those reported for unsubstituted theophylline (Sutor, 1958) and the possibility of intra- and intermolecular hydrogen bonding. These data will be used to generate information concerning the effects of the substituents on receptor affinities of 7,8-disubstituted theophylline derivatives.

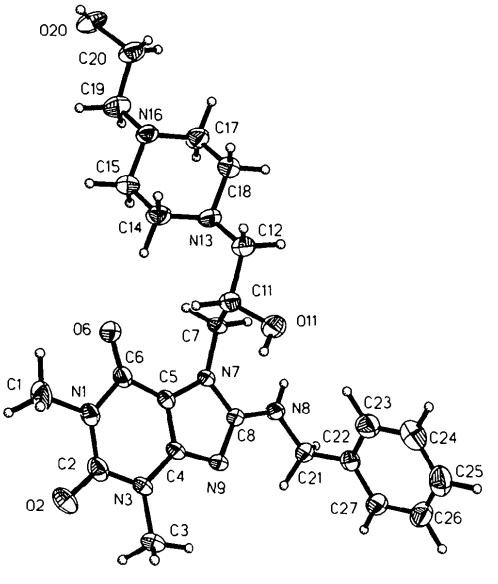


Fig. 1. A view of the molecule with the atomic labelling. Non-H atoms are represented by displacement ellipsoids of 50% probability.

Experimental

Preparation of the title compound was performed according to the published procedure (Gorczyca, Pawłowski & Łucka-Sobstel, 1982). Crystals of the racemate of the two enantiomers were grown by slow evaporation from ethanol solution.

Crystal data

$C_{23}H_{33}N_7O_4$
$M_r = 471.56$
Triclinic
$P\bar{1}$
$a = 9.511\ (1)$ Å
$b = 11.716\ (1)$ Å
$c = 12.138\ (2)$ Å
$\alpha = 67.68\ (2)°$
$\beta = 73.19\ (2)°$
$\gamma = 73.45\ (2)°$
$V = 1174.1\ (4)$ Å^3
$Z = 2$
$D_x = 1.334$ Mg m^{-3}
Cu $K\alpha$ radiation
$\lambda = 1.54184$ Å
Cell parameters from 23 reflections
$\theta = 10–50°$
$\mu = 0.681$ mm^{-1}
$T = 293$ K
Plate
0.30 × 0.20 × 0.10 mm
Colourless

Data collection

Kuma KM-4 diffractometer
$\omega/2\theta$ scans
Absorption correction: none
5155 measured reflections
4840 independent reflections
3361 observed reflections $[F > 4\sigma(F)]$
$R_{int} = 0.0206$
$\theta_{max} = 82°$
$h = -11 \rightarrow 11$
$k = -14 \rightarrow 14$
$l = 0 \rightarrow 15$
2 standard reflections monitored every 100 reflections
intensity decay: none

Refinement

Refinement on F
$R = 0.0552$
$wR = 0.0610$
$S = 1.98$
3361 reflections
317 parameters
$w = 5.3774/[\sigma^2(F_o) + 0.00019F_o^2]$
$(\Delta/\sigma)_{max} = 0.001$
$\Delta\rho_{max} = 0.31$ e Å^{-3}
$\Delta\rho_{min} = -0.22$ e Å^{-3}
Extinction correction: $F_c^* = F_c(1-gF_c^2/\sin\theta)$
Extinction coefficient: $g = 1.3\ (2) \times 10^{-6}$
Atomic scattering factors from *SHELX*76 (Sheldrick, 1976)

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

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

	x	y	z	U_{eq}
N1	0.6930 (3)	0.3208 (2)	0.0407 (2)	0.0363 (4)
N3	0.5540 (3)	0.4045 (2)	0.1974 (2)	0.0339 (4)
N7	0.2820 (2)	0.3543 (2)	0.0855 (2)	0.0279 (4)
N8	0.0500 (3)	0.4224 (2)	0.2044 (2)	0.0379 (6)
N9	0.2848 (2)	0.4274 (2)	0.2326 (2)	0.0318 (4)
N13	0.2494 (3)	0.1434 (2)	−0.1284 (2)	0.0376 (6)

N16	0.3585 (3)	0.1257 (2)	−0.3708 (2)	0.0365 (4)
O2	0.8072 (2)	0.3765 (2)	0.1485 (2)	0.0537 (6)
O6	0.5837 (2)	0.2708 (2)	−0.0758 (2)	0.0450 (4)
O11	0.2228 (3)	0.1060 (2)	0.1916 (2)	0.0484 (6)
O20	0.4168 (3)	0.0983 (2)	−0.6716 (2)	0.0535 (6)
C1	0.8413 (3)	0.2772 (3)	−0.0268 (3)	0.0485 (9)
C2	0.6911 (3)	0.3675 (3)	0.1301 (3)	0.0376 (7)
C3	0.5471 (4)	0.4558 (3)	0.2917 (3)	0.0447 (8)
C4	0.4259 (3)	0.3948 (2)	0.1730 (2)	0.0290 (4)
C5	0.4321 (3)	0.3499 (2)	0.0829 (2)	0.0283 (4)
C6	0.5668 (3)	0.3103 (2)	0.0084 (2)	0.0316 (4)
C7	0.2305 (3)	0.2978 (2)	0.0197 (2)	0.0298 (4)
C8	0.2005 (3)	0.4001 (2)	0.1773 (2)	0.0284 (4)
C11	0.2822 (3)	0.1544 (3)	0.0642 (2)	0.0356 (6)
C12	0.2298 (4)	0.0872 (3)	0.0035 (2)	0.0400 (7)
C14	0.4064 (3)	0.1405 (3)	−0.1896 (3)	0.0414 (8)
C15	0.4211 (4)	0.1980 (3)	−0.3274 (3)	0.0440 (7)
C17	0.2005 (4)	0.1297 (3)	−0.3105 (3)	0.0461 (8)
C18	0.1851 (4)	0.0749 (3)	−0.1743 (3)	0.0450 (8)
C19	0.3756 (4)	0.1776 (3)	−0.5039 (3)	0.0469 (7)
C20	0.3307 (4)	0.0948 (3)	−0.5537 (3)	0.0487 (8)
C21	−0.0354 (3)	0.4702 (3)	0.3028 (2)	0.0378 (7)
C22	−0.0849 (3)	0.3715 (3)	0.4225 (2)	0.0350 (6)
C23	−0.0726 (4)	0.2479 (3)	0.4319 (3)	0.0458 (8)
C24	−0.1219 (4)	0.1614 (3)	0.5444 (3)	0.0576 (8)
C25	−0.1824 (4)	0.1980 (4)	0.6469 (3)	0.0554 (8)
C26	−0.1949 (4)	0.3217 (4)	0.6375 (3)	0.0532 (8)
C27	−0.1470 (3)	0.4074 (3)	0.5256 (3)	0.0439 (8)

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

N1—C1	1.469 (4)	N7—C8	1.360 (3)
N1—C2	1.382 (4)	N8—C8	1.343 (3)
N1—C6	1.415 (3)	N9—C4	1.351 (3)
N3—C2	1.373 (4)	N9—C8	1.347 (3)
N3—C3	1.461 (3)	O2—C2	1.227 (3)
N3—C4	1.378 (3)	O6—C6	1.228 (3)
N7—C5	1.404 (3)	C4—C5	1.363 (3)
N7—C7	1.459 (3)	C5—C6	1.409 (3)
C1—N1—C2	116.5 (2)	N3—C4—N9	125.2 (2)
C1—N1—C6	117.0 (2)	N3—C4—C5	121.4 (2)
C2—N1—C6	126.5 (2)	N9—C4—C5	113.4 (2)
C2—N3—C3	119.2 (2)	N7—C5—C4	104.9 (2)
C2—N3—C4	119.4 (2)	N7—C5—C6	131.6 (2)
C3—N3—C4	121.4 (2)	C4—C5—C6	123.5 (2)
C5—N7—C7	125.9 (2)	N1—C6—O6	120.1 (2)
C5—N7—C8	105.2 (2)	N1—C6—C5	111.6 (2)
C7—N7—C8	127.8 (2)	O6—C6—C5	128.3 (3)
C4—N9—C8	103.0 (2)	N7—C8—N8	122.5 (2)
N1—C2—N3	117.5 (2)	N7—C8—N9	113.4 (2)
N1—C2—O2	121.5 (3)	N8—C8—N9	123.9 (2)
N3—C2—O2	121.0 (3)		
C8—N7—C7—C11	−103.5 (3)	N7—C8—N8—C21	179.5 (3)
N7—C7—C11—C12	178.2 (2)	C8—N8—C21—C22	−96.4 (3)
C7—C11—C12—N13	46.0 (4)	N8—C21—C22—C27	170.2 (3)
C11—C12—N13—C14	63.1 (4)		

The positions of the H atoms of the amino and hydroxy groups were located from difference electron-density maps and were refined; all other H atoms were placed in calculated positions and refined using a riding model. Isotropic displacement parameters of $1.5U_{eq}$ of their respective parent C atoms were used for all H atoms.

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.

The crystallographic studies were supported by grant No. 3 0302 91 01 from the Polish State Committee for Scientific Research.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: BM1000). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Anti-Inflammatory Drugs. II. Salt of 2-(2,6-Dichlorophenylamino)phenylacetic Acid with Diethanolamine

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Abstract

The structure of the title salt, bis(2-hydroxyethyl)-ammonium 2-(2,6-dichlorophenylamino)phenylacetate, $C_4H_{12}NO_2^+.C_{14}H_{10}Cl_2NO_2^-$, has been determined by X-ray diffraction. The asymmetric unit consists of one cation and one anion. The structural unit is best