some lines and planes and the angles between them are given in Table 3. An extended and modified version of *ORTEP* (Johnson, 1970) was used for the projection of the asymmetric unit of the title compound. The configuration of the two chiral centers is established as 1*R*,2*S*, which is in agreement with the NMR study. The projection and the atomic labeling are given in Fig. 1. In this figure two Cl atoms are displayed to demonstrate the hydrogen bonding. The second Cl atom belongs to a neighbouring molecule. In Fig. 2 the cell contents are displayed. This figure shows some of the hydrogen bonding, but the way in which the hydrogen bonding connects molecules in different cells is displayed in Fig. 3.

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Acta Cryst. (1992). C**48**, 347–350

Structure of 2-Amino-6-dimethylamino-4-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3,5-triazine

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(*Received* 16 *July* 1991; *accepted* 21 *August* 1991)

Abstract. $C_{15}H_{23}N_5$, $M_r = 273.4$, triclinic, $P\bar{1}$, $a = 6.907\ (6)$, $b = 10.260\ (5)$, $c = 10.619\ (2)$ Å, $\alpha = 104.64\ (4)$, $\beta = 91.61\ (7)$, $\gamma = 104.88\ (5)°$, $V = 700.2\ (14)$ Å^3, $Z = 2$, $D_m = 1.295$, $D_x = 1.296$ Mg m^{-3}, λ(Cu $K\alpha$) = 1.54184 Å, $\mu = 0.648$ mm^{-1}, $F(000) = 296$, $T = 293$ K, final $R = 0.059$ for 1510 observed reflections. In pyrimidine analogs of this class of antifolate agents, a lipophilic substituent at position 5 disrupts the ring planarity [Cody (1986). *J. Mol. Graphics*, **4**(1), 69–73]. Here, the adamantyl substituent at position 4 does not have a similar effect. The adamantyl assumes one of the two observed possible conformations relative to the triazine ring.

Introduction. Dihydrofolate reductase [5,6,7,8-tetrahydrofolate:NADP$^+$ oxidoreductase (E.C. 1.5.1.3)], an enzyme which reduces dihydrofolic to tetrahydrofolic acid, is a protein of prime importance in biochemistry and medicinal chemistry (Blakley, 1969). It is used as a target for several antibacterial and antineoplasmic (antitumor) drugs. The activity of these drugs is due to selective inhibition of the enzyme from species to species (Baccarani, Daluge & King, 1982; Hitchings & Smith, 1980). Unfortunately, the exact molecular mechanism of selective inhibition is not yet known, despite extensive efforts.

The discovery that diamino-*s*-triazines interfere with folic acid metabolism triggered research on the antifolate activity of this class of compounds and has shown promise in cancer chemotherapy (Modest, Foley, Pechet & Farber, 1952). A conclusion drawn from these studies is that for several antifolates the extent of their uptake and their growth inhibitory potency on tumor cells, as well as their affinity to dihydrofolate reductase (DHFR), correlate well with lipophilicity (Greco & Hakala, 1980). In the course of our investigations on compounds containing adamantane rings (Antoniadou-Vyza & Foscolos, 1986; Garoufalias, Vyza, Fytas, Foscolos & Chytiroglou, 1988) we considered it likely that attachment of this group to a triazine ring would allow it to make effective use of the enzyme hydrophobic cavity. In addition, the absence of any

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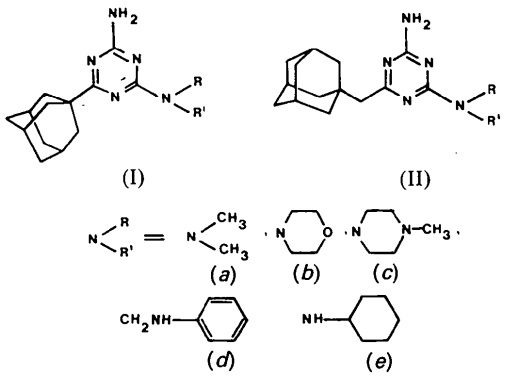
information on the antifolate activity of amino-substituted analogs, in contrast to the plethora of similar information on the diamino derivatives, prompted us to attempt substitution on the 6-amino nitrogen of the triazine molecule. Therefore, possible DHFR inhibitors of the general types I and II have been synthesized as antitumor, antibacterial and antifungal agents.



All compounds are being tested for DHFR-binding affinity and pharmacological properties (Tsitsa, Antoniadou-Vyza, Hamodrakas, Eliopoulos, Tsantili-Kakoulidou, Lada-Hytiroglou, Chinou, Hempel, Camerman, Ottensmeyer & Vanden Berghe, 1991). In order to understand the observed variation in biological activity and compare structure and binding with other antifolate ligands (Cody, 1984, 1986), the crystal structure determination and conformational analysis of both active and inactive lipophilic compounds is underway (Hamodrakas, Hempel, Camerman, Camerman, Ottensmeyer, Tsitsa & Antoniadou-Vyza, 1991). The title compound (Ia) is a member of the type I series.

Experimental. Crystals grew from a methanol solution. Size of crystal used 0.50 × 0.50 × 0.20 mm, Enraf–Nonius CAD-4 diffractometer, graphite-monochromatized Cu $K\alpha$ radiation, 3ω–4θ scans. Lattice parameters were obtained from 22 reflections with $16.9 < \theta < 27.5°$. Index range 0 to 8 (h), −12 to 12 (k), −12 to 12 (l). For every reflection its Friedel equivalent was measured at the alternative $-\theta$ position. 4984 reflections were collected (all available) with $2 < 2\theta < 130°$, of which after merging (R_{int} = 0.073) 2380 were independent and 2259 had $I > \sigma(I)$. Four strong reflections [with $I > 40\sigma(I)$] used as intensity standards. They were measured every 18000 s with an average final loss of intensity of 2.8%. Corrections applied for Lorentz, polarization, radiation damage and absorption effects (six reflections with $82 < \chi < 85°$ used for semi-empirical correction using ψ-scan values; correction factors maximum = 0.9972 and minimum = 0.8016). The

Table 1. *Fractional coordinates* ($\times 10^4$) *of non-hydrogen atoms and equivalent isotropic temperature factors* (Å^2) *with e.s.d.'s given in parentheses*

Atoms refined anisotropically. The equivalent isotropic displacement parameter given here is defined as $(4/3)[a^2B(1,1) + b^2B(2,2) + c^2B(3,3) + ab(\cos\gamma)B(1,2) + ac(\cos\beta)B(1,3) + bc(\cos\alpha)B(2,3)]$.

	x	y	z	B
N(1)	5012 (5)	3517 (3)	8475 (3)	3.88 (8)
C(2)	6784 (6)	3989 (4)	9158 (3)	3.61 (9)
N(3)	7310 (4)	3770 (3)	10315 (3)	3.50 (7)
C(4)	5751 (5)	2973 (4)	10763 (3)	3.41 (9)
N(5)	3917 (5)	2451 (3)	10175 (3)	3.77 (7)
C(6)	3584 (6)	2729 (4)	9030 (3)	3.71 (9)
N(7)	8279 (5)	4789 (3)	8640 (3)	4.56 (8)
N(8)	1734 (5)	2219 (3)	8400 (3)	4.29 (8)
C(9)	6086 (6)	2654 (4)	12054 (3)	3.33 (8)
C(10)	5481 (6)	1064 (4)	11844 (4)	3.98 (9)
C(11)	8245 (6)	3246 (4)	12694 (4)	4.2 (1)
C(12)	4711 (6)	3285 (4)	13014 (3)	4.04 (9)
C(13)	5651 (7)	692 (4)	13145 (4)	4.4 (1)
C(14)	7836 (7)	1295 (4)	13758 (4)	4.7 (1)
C(15)	8450 (6)	2862 (4)	13987 (4)	4.3 (1)
C(16)	7070 (7)	3498 (4)	14917 (4)	4.7 (1)
C(17)	4902 (6)	2912 (4)	14309 (4)	4.3 (1)
C(18)	4294 (6)	1333 (4)	14077 (4)	4.5 (1)
C(19)	1270 (6)	2447 (5)	7154 (4)	4.8 (1)
C(20)	90 (6)	1385 (4)	8952 (4)	4.8 (1)

Table 2. *Selected bond distances* (Å), *bond angles and dihedral angles* (°) *with e.s.d.'s given in parentheses*

N(1)—C(2)	1.314 (6)	C(9)—C(11)	1.524 (7)
N(1)—C(6)	1.356 (6)	C(9)—C(12)	1.548 (7)
C(2)—N(3)	1.359 (6)	C(10)—C(13)	1.533 (7)
C(2)—N(7)	1.367 (6)	C(11)—C(15)	1.533 (7)
N(3)—C(4)	1.352 (6)	C(12)—C(17)	1.528 (7)
C(4)—N(5)	1.312 (6)	C(13)—C(14)	1.532 (8)
C(4)—C(9)	1.513 (6)	C(13)—C(18)	1.527 (8)
N(5)—C(6)	1.344 (6)	C(14)—C(15)	1.501 (7)
C(6)—N(8)	1.336 (6)	C(15)—C(16)	1.535 (8)
N(8)—C(19)	1.442 (7)	C(16)—C(17)	1.519 (8)
N(8)—C(20)	1.468 (7)	C(17)—C(18)	1.518 (7)
C(9)—C(10)	1.532 (7)		

C(2)—N(1)—C(6)	113.8 (4)	C(4)—N(5)—C(6)	116.7 (4)
N(1)—C(2)—N(3)	127.8 (4)	N(1)—C(6)—N(5)	124.0 (4)
N(1)—C(2)—N(7)	116.1 (4)	N(1)—C(6)—N(8)	117.4 (4)
N(3)—C(2)—N(7)	116.1 (4)	N(5)—C(6)—N(8)	118.6 (4)
C(2)—N(3)—C(4)	112.5 (4)	C(6)—N(8)—C(19)	121.8 (5)
N(3)—C(4)—N(5)	125.3 (4)	C(19)—N(8)—C(20)	117.3 (5)
N(3)—C(4)—C(9)	119.0 (4)	C(6)—N(8)—C(20)	120.8 (4)
N(5)—C(4)—C(9)	115.7 (4)		

N(3)—C(4)—C(9)—C(10)	−124.23 (35)	N(3)—C(4)—C(9)—C(12)	117.93 (35)
N(5)—C(4)—C(9)—C(10)	56.86 (42)	N(5)—C(4)—C(9)—C(12)	−60.98 (40)
N(3)—C(4)—C(9)—C(11)	−2.44 (47)	N(1)—C(6)—N(8)—C(19)	2.18 (53)
N(5)—C(4)—C(9)—C(11)	178.64 (31)	N(1)—C(6)—N(8)—C(20)	−178.48 (33)

structure was solved in $P\bar{1}$ by direct methods using the programs of the *SDP* package (B. A. Frenz & Associates, Inc., 1985). 13 non-hydrogen atoms were thus located. Subsequent difference Fourier maps showed all atoms including hydrogens. The hydrogens of C(19) and C(20) were refined with occupancy 0.5, because another five hydrogen positions had been found at about 60° with respect to the original hydrogen positions. The sixth hydrogen position was calculated and fixed. 272 parameters (anisotropic

thermal parameters for non-hydrogens and isotropic for hydrogens) were included in full-matrix least-squares refinements (B. A. Frenz & Associates, Inc., 1985) on F using 1510 observed reflections with $0.05 < \sin\theta/\lambda < 0.52$ Å^{-1}; reflections with $0.52 < \sin\theta/\lambda < 0.59$ Å^{-1} were not included in the refinement because the R factor for these was 0.18. The authors believe that this is due to the variations of the peak profiles which were not taken into account during the data reduction procedures; unit weights. Atomic scattering factors were taken from a table compiled by Cromer & Waber (1974). Final $R = 0.059$, maximum $(\Delta/\sigma) = 0.05$, $S = 1.029$. In final difference Fourier map $(\Delta\rho)_{min} = -0.20$ and $(\Delta\rho)_{max} = 0.19$ e Å^{-3}.

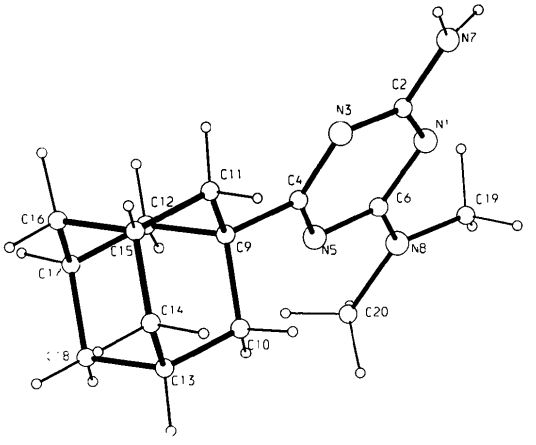


Fig. 1. *PLUTO*78 (Motherwell & Clegg, 1978) drawing of the title molecule showing the numbering of the atoms.

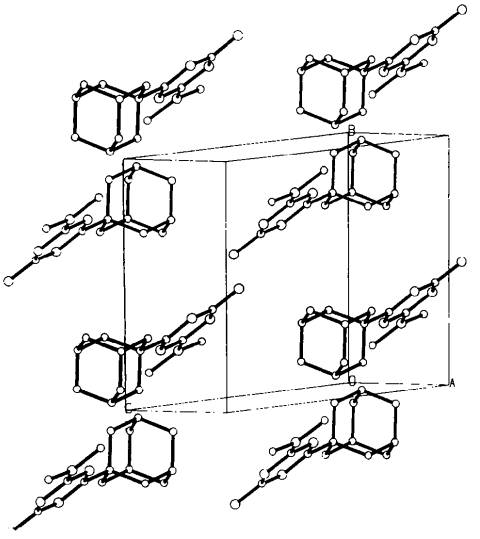


Fig. 2. *a*-axis projection drawn with *PLUTO*78 showing the crystal packing. Hydrogens have been omitted for clarity.

Discussion. Positional and isotropic thermal parameters of non-hydrogen atoms are listed in Table 1, bond lengths, angles and selected torsion angles are shown in Table 2.* A perspective view of the molecule showing the atomic numbering scheme used is given in Fig. 1, and the unit-cell packing is depicted in Fig. 2.

In pyrimidine analogs of I and II a lipophilic substituent at position 5 disrupts the ring planarity (Cody, 1986). The adamantyl substituent at position 4 in the title compound does not have a similar effect: the atoms of the triazine ring are coplanar to within 0.2 Å. Only two possible orientations of the adamantyl moiety relative to the triazine ring have been observed in the crystal structures of 4-adamantyltriazines; one has a C—C bond of the adamantyl moiety in an eclipsed conformation relative to N(3)—C(4) of the triazine ring [in 2-amino-6-morpholino-4-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3,5-triazine (I*b*); Tsitsa *et al.*, 1991] and the other a C—C bond of adamantyl in an eclipsed conformation relative to C(4)—N(5) of the triazine ring [in 2-amino-6-cyclohexylamino-4-(tricyclo[3.3.1.1^{3,7}]dec-1-yl)-1,3,5-triazine (I*e*); Tsitsa *et al.*, 1991]. The two conformations differ by a relative rotation of 60° of the symmetrical adamantyl moiety around the C(4)—C(9) bond which connects the adamantyl substituent to the triazine ring. Interestingly, both are simultaneously observed in the crystal structure of 2-amino-6-*N*-methylpiperazino-4-(tricyclo-[3.3.1.1^{3,7}]dec-1-yl)-1,3,5-triazine (I*c*) (Hamodrakas *et al.*, 1991) which crystallizes in space group $R\bar{3}$. Conformational analysis, utilizing semi-empirical energy calculations, suggests that both are energetically favourable (the only energy minima), differing slightly in energy (Hamodrakas, 1991). Here, C(9)—C(11) of adamantyl is eclipsed relative to N(3)—C(4) of the *s*-triazine ring (Table 2).

The conformation of substituents at position 6 of the triazine ring is determined by the torsion angle N(1)—C(6)—N(8)—C(19). In related structures this angle is always close to 0° and here is 2.2 (5)°.

We would like to thank Dr E. Eliopoulos for helpful discussions.

* Lists of structure factors, anisotropic thermal parameters, H-atom parameters and torsion angles have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54512 (30 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: MU0281]

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Acta Cryst. (1992). C**48**, 350–352

Structure of *p-tert*-Butylhexahomotrioxacalix[3]arene

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(*Received* 30 *May* 1991; *accepted* 28 *August* 1991)

Abstract. 7,15,23-Tri-*tert*-butyl-25,26,27-trihydroxy-2,3,10,11,18,19-hexahomo-3,11,19-trioxacalix[3]-arene, $C_{36}H_{48}O_6$, $M_r = 576.4$, orthorhombic, *Pnma*, $a = 9.348$ (1), $b = 16.604$ (2), $c = 21.992$ (3) Å, $V = 3413.5$ (8) Å^3, $Z = 4$, $D_x = 1.12$ g cm^{-3}, graphite-monochromated Cu $K\alpha$, $\lambda = 1.54178$ Å, μ(Cu $K\alpha$) $= 5.65$ cm^{-1}, $F(000) = 1248$, $T = 288$ K, final $R = 0.054$ for 1858 reflections. There is a mirror plane and pseudo C_{3v} symmetry in the molecule. This inclusion molecule adopts a cone conformation and its cavity is too shallow to capture guest molecules.

Introduction. It is well known that calixarenes are cyclic phenol-methylene oligomers which are capable of including small molecules (Gutsche, 1989). The title compound, *p-tert*-butylhexahomotrioxacalix-[3]arene, is one of the calixarenes which can be made from the condensation of *p-tert*-butylphenol and paraformaldehyde (Dhawan & Gutsche, 1983). The X-ray structure analysis reported here was undertaken to determine the molecular conformation.

Experimental. Colorless pillar crystals from *m*-xylene solution evaporation at room temperature. Crystal $0.1 \times 0.1 \times 0.5$ mm. Cell dimensions: least squares on 25 reflections, $47 < 2\theta < 54°$. Systematic absences ($0kl$, $k + l = 2n$; $hk0$, $h = 2n$) indicated the space group to be *Pnma* or $Pn2_1a$; the final structure was refined as *Pnma*. Rigaku AFC-5 automated diffractometer, $2\theta_{max} = 120°$ ($-10 \le h \le 0$, $0 \le k \le 19$, $0 \le l \le 25$), ω–2θ-scan mode. A total of 3156 reflections collected, 2870 unique reflections measured, 2105 considered observed [$|F_o| > 3\sigma(F_o)$]. Three standard reflections ($11\bar{2}$, $3\bar{1}\bar{1}$ and $1\bar{5}0$) monitored every 200 reflections; intensity decreased less than 3% during the data collection. No corrections for absorption and extinction. Structure solved by direct methods with *SHELXS*86 (Sheldrick, 1985). Positional and thermal parameters refined by full-matrix least-squares method with *SHELX*76 (Sheldrick, 1976); H atoms, except those of the disordered C(11*B*) methyl group, located on difference Fourier maps using programs of *The Universal Crystallographic Computing System–Osaka* (1979); non-H atoms refined with anisotropic temperature factors and H-atom positions refined with fixed isotropic temperature factors. Final $R = 0.054$, $wR = 0.058$ for 1858 reflections, $S = 0.981$ for 271 parameters; function mini-

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