C17	−0.2385 (5)	0.6830 (3)	0.2361 (6)	0.063 (2)
O18	−0.1003 (4)	0.5172 (2)	0.0880 (5)	0.083 (2)
C19	0.4340 (5)	0.8502 (3)	0.3582 (6)	0.054 (2)
C20	0.4882 (5)	0.7811 (3)	0.4135 (5)	0.053 (2)
C21	0.4412 (4)	0.7088 (3)	0.3490 (5)	0.043 (2)
C22	0.3336 (4)	0.7081 (3)	0.2229 (5)	0.034 (2)
C23	0.5019 (5)	0.6356 (3)	0.4017 (5)	0.054 (2)
C24	0.4630 (5)	0.5661 (3)	0.3315 (6)	0.057 (2)
C25	0.3623 (5)	0.5667 (3)	0.2054 (5)	0.045 (2)
C26	0.2987 (4)	0.6349 (2)	0.1528 (5)	0.035 (2)
O27	0.3329 (4)	0.4956 (2)	0.1386 (4)	0.065 (2)
H14	0.0271	0.6426	0.0512	0.080
H26	0.2290	0.6332	0.0667	0.080
H18	−0.072 (6)	0.508 (4)	0.021 (7)	0.080
H27	0.256 (6)	0.496 (3)	0.063 (6)	0.080

Table 2. *Selected geometric parameters* (°)

Bond angles			
Splay			
C4—C3—C22	124.5 (3)	C4—C9—C10	125.2 (4)
O1—C2—C19	113.4 (4)	O7—C8—C13	112.7 (4)
Hinge			
C3—C4—C9	110.5 (3)	O1—C6—O7	107.3 (4)
Dihedral angles			
Connector			
C22—C3—C4—C9	98.8 (5)	C3—C4—C9—C10	−93.3 (4)
O1—C2—C3—C22	174.4 (5)	O7—C8—C9—C10	−177.9 (3)
C6—O1—C2—C19	−178.7 (5)	C6—O7—C8—C13	177.6 (3)
C2—O1—C6—C5	−28.1 (6)	C5—C6—O7—C8	34.0 (5)
O1—C2—C3—C4	−4.7 (7)	O7—C8—C9—C4	1.8 (6)
C6—O1—C2—C3	0.1 (7)	C6—O7—C8—C9	−2.8 (5)
Naphthalene components			
C2—C3—C22—C26	−169.9 (5)	C8—C9—C10—C14	175.7 (4)
C4—C3—C22—C26	9.1 (7)	C4—C9—C10—C14	−4.1 (6)
C20—C21—C22—C26	173.4 (5)	C14—C10—C11—C12	−175.9 (4)
C23—C21—C22—C3	177.0 (5)	C9—C10—C11—C17	−176.6 (4)
C19—C2—C3—C22	−7.0 (8)	C13—C8—C9—C10	1.6 (6)
C3—C2—C19—C20	0.7 (9)	C9—C8—C13—C12	2.5 (6)
C2—C19—C20—C21	3.1 (9)	C11—C12—C13—C8	−2.8 (6)
C19—C20—C21—C23	176.7 (5)	C17—C11—C12—C13	−179.2 (4)
C20—C21—C23—C24	−174.4 (5)	C12—C11—C17—C16	176.5 (4)
C21—C23—C24—C25	0.3 (9)	C15—C16—C17—C11	−0.1 (7)
C23—C24—C25—C26	−2.2 (9)	C14—C15—C16—C17	1.3 (8)
C24—C25—C26—C22	1.0 (8)	C10—C14—C15—C16	−0.6 (7)
C3—C22—C26—C25	−178.7 (5)	C9—C10—C14—C15	177.7 (4)
H atoms H14 and H26			
C21—C22—C26—H26	−178.0 (3)	C11—C10—C14—H14	178.7 (2)
C24—C25—C26—H26	−179.0 (4)	H14—C14—C15—C16	179.4 (4)

All H atoms were located by difference Fourier synthesis. Only the positions of H18 and H27 were refined, as free rotation is possible around the C—OH bonds.

Data collection: *SHELXTL-Plus* (Sheldrick, 1990). Cell refinement: *SHELXTL-Plus*. Data reduction: *SHELXTL-Plus*. Program(s) used to solve structure: *SHELXTL-Plus*. Program(s) used to refine structure: *SHELXTL-Plus*. Molecular graphics: *SHELXTL-Plus* and *INSIGHTII/DISCOVER* (Biosym Technologies, San Diego, CA, USA).

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Lists of structure factors, anisotropic displacement parameters, H-atom coordinates, bond distances and angles, and torsion angles have been deposited with the IUCr (Reference: SZ1012). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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1-(*p*-Carbamoylphenyl)-3,3-dimethyltriazene, an Antitumour Agent

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Abstract

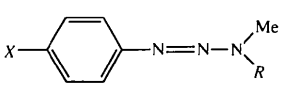
In the crystal structure of the title compound, 4-(3,3-dimethyl-1-triazeno)benzamide, $C_9H_{12}N_4O$, (2), the N=N double bond [1.282 (8) Å] is 0.030 Å shorter than the N—N single bond [1.312 (8) Å], but both bonds are shorter than an isolated N—N single bond suggesting that there is double-bond character in each N—N bond, although it is unequally distributed. The molecule adopts a *trans* geometry around the N=N bond, but there is a significant deviation from planarity between the benzene ring and the plane of the triazene moiety. Compound (2) forms chains in the solid state in which the molecules are linked by C=O···H—N hydrogen bonds between carbamoyl groups. These chains are cross-linked into sheets by hydrogen bonding between the second N—H moiety and triazene units in adjacent chains.

Comment

1-Aryl-3,3-dialkyltriazenes, Ar—N=N—NR_2, represent a well known class of antitumour agents (Vaughan, 1990). The most familiar member of this drug family is DTIC [5-(3,3-dimethyltriazen-1-yl)imidazole-4-

carboxamide (dacarbazine); NSC 45388], which has been used primarily in the treatment of human malignant melanoma (Lucas & Huang, 1982). The development of a second-generation triazene, prompted by the dose-limiting side effects of DTIC, has been a focus for recent study (Wilman, 1988) and has led to the successful Phase I clinical trial of *p*-(3,3-dimethyltriazen-1-yl)benzoic acid [(1); CB10-277; Foster *et al.*, 1993], which was followed up with the Phase II clinical trial (Bleehen *et al.*, 1994). A more recent development was the selection of the triazene pro-drug 8-carbamoyl-3-methylimidazo[5,1-*d*]-1,2,3,5-tetrazin-4(3*H*)-one (temozolomide; CCRG 81045; NSC 362856) for clinical trials. Temozolomide has shown promising antitumour activity against high-grade gliomas and melanoma (Newlands *et al.*, 1992).

Extensive studies with a series of aryldialkyltriazenes led to the significant conclusion that only arylalkyltriazenes that can metabolize *in vivo* to an aryl-N^3-monomethyltriazene have antitumour properties (Connors, Goddard, Merai, Ross & Wilman, 1976). Further study confirmed the relationship between metabolism and antitumour activity (Wilman *et al.*, 1984). A key compound in these metabolism studies has been the title compound, 1-*p*-(carbamoylphenyl)-3,3-dimethyltriazene [(2); DM-$CONH_2$], which possesses antileukaemic activity and has been shown to require metabolic activation by liver homogenate supernatant and cofactors in order to exert *in vitro* cytotoxic effects on tumour cells (Sava, Giraldi, Lassiani, Nisi & Farmer, 1982; Abel, Connors & Giraldi, 1977). In view of the central importance of DM-$CONH_2$ and the value of knowledge of molecular structure to the rational design of new drugs, we have undertaken the crystal structure determination of the triazene (2).



(1) X = COOH; R = Me
(2) X = $CONH_2$; R = Me
(3) X = NO_2; R = Me
(4) X = CN; R = Me
(5) X = CH_3; R = H

The molecular structure of (2) is shown in Fig. 1. The results show that the N2—N3 bond is shorter than the N3—N4 bond by 0.03 Å and that the molecule, as expected, adopts a *trans* geometry around the N2—N3 bond.

A frequent consideration with molecules of this nature is the question of planarity, particularly any departure from planarity. The results show that the plane of the three non-H atoms of the amide moiety (O—C7—N1) is very close to being coplanar with the benzene ring; the dihedral angle between the planes is found to be 1.0 (5)°. However, deviation from planarity is much more pronounced at the triazene end of the molecule. The dihedral angle between the N2—N3—N4 and the C8—N4—C9 planes is found to be 5.6 (7)°. The most significant deviation from planarity is between the plane of the benzene ring and the N2—N3—N4 plane, which form a dihedral angle of 17.8 (5)°. A viable explanation for this severe distortion from planarity can be found in the view of the extended crystal-lattice structure (Fig. 2).

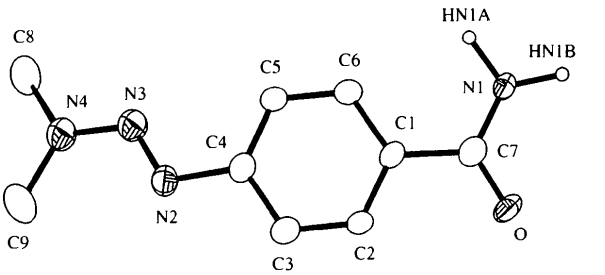


Fig. 1. Perspective view of (2). Displacement ellipsoids are drawn at the 30% probability level.

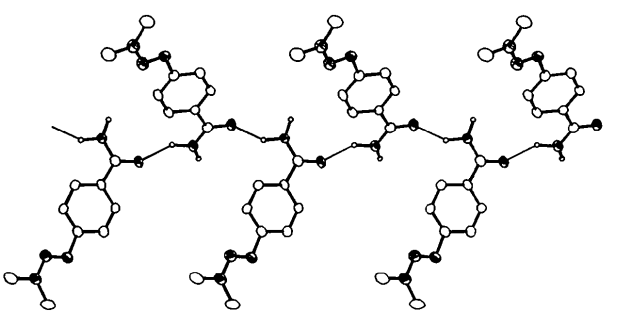
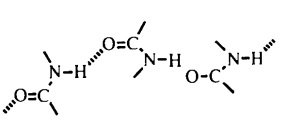


Fig. 2. The linear chain formed by self-assembly of (2). Displacement ellipsoids are drawn at the 30% probability level.

Fig. 2 shows that molecules of (2) form hydrogen bonds between their amide groups in a similar fashion to the intermolecular interactions found in protein-like molecules. A hydrogen bond is formed between the carbonyl O atom (O at C7) and a proton at N1 (HN1*A*). Each amide group is able to participate in two diametrically opposing hydrogen bonds resulting in an infinite chain of hydrogen-bonded amide groups:



The dimethyltriazenylphenyl groups hang off the amide chain at regular intervals. These chains are cross-linked by hydrogen bonds formed between the second N—H moiety and atom N2 of the triazene moieties in adjacent chains (Fig. 3). The significant deviation from planarity of the triazene group and the aromatic ring could be a consequence of the hydrogen-bonding interactions.

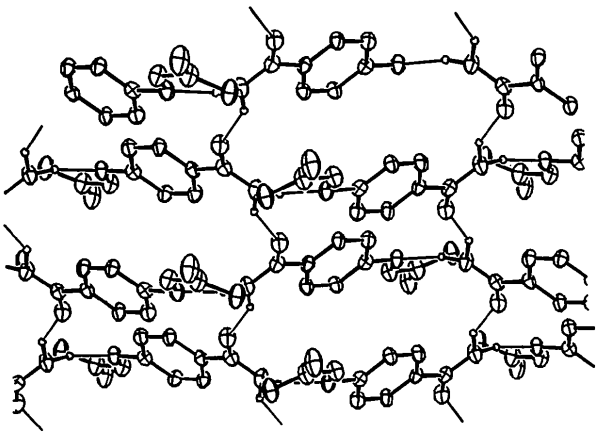
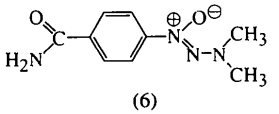


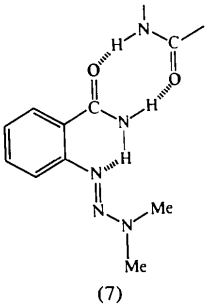
Fig. 3. Sheets formed by cross-linking of the chains illustrated in Fig. 2. Displacement ellipsoids are drawn at the 30% probability level.

An alternative explanation for the deviation from planarity is steric crowding between N3 and the H atom at C5, which is clearly visible in the opening of the C5—C4—N2 angle. A similar effect was observed in the crystal structure of 3-methyl-1-(*p*-tolyl)triazene, (5) (Randall, Schwalbe & Vaughan, 1984), and analogous enlargement of the C5—C4—N2 angle has been observed in other related triazenes (Fronczek, Hansch & Watkins, 1988).

In conclusion, it is useful to compare the bond lengths observed here for compound (2) with those reported earlier for similar triazenes. The *ortho* isomer of (2), 2-(3,3-dimethyl-1-triazeno)benzamide, (7), has been reported (Edwards, Chapuis, Templeton & Zalkin, 1977) and has been found to have quite a different structure. Molecules of (7) are paired together as dimers, held together by hydrogen bonds between the carbonyl O atom and one of the NH protons of the amide group. The other amide proton is intramolecularly hydrogen bonded to atom N2 of the triazene moiety, as shown below.



(6)



(7)

Two other aryldimethyltriazene crystal structures have been reported: 1-*p*-nitrophenyl-3,3-dimethyltriazene, (3) (Neidle & Wilman, 1992), and 1-*p*-cyanophenyl-3,3-dimethyltriazene, (4) (Fronczek, Hansch & Watkins, 1988). Neidle & Wilman (1992) also report the crystal structure of an analogue with a *p*-carbamoyl group, 1-(*p*-carbamoylphenyl)-3,3-dimethyltriazene 1-oxide, (6). The only other related report is the crystal structure of the N^3-monomethyltriazene 1-*p*-tolyl-3-methyltriazene, (5) (Randall, Schwalbe & Vaughan, 1984). Table 3 presents a bond-length comparison for these triazenes; the bond lengths are consistent with the assigned structures. In all of these compounds the N2—N3 bond is shorter than the N3—N4 bond. Although this difference between the two N—N bond lengths indicates greater double-bond character in the N2—N3 bond, both bonds N2—N3 and N3—N4 are shorter than an isolated N—N single bond (*ca.* 1.45 Å), suggesting that there is double-bond character in each, although it is unequally distributed.

Experimental

1-(*p*-Carbamoylphenyl)-3,3-dimethyltriazene, (2), was synthesized by diazotization of *p*-aminobenzamide in hydrochloric acid, followed by coupling of the obtained *p*-carbamoylbenzene diazonium chloride with dimethylamine according to the method of described by Connors, Goddard, Merai, Ross & Wilman (1976). The product was recrystallized from water as yellow needles (m.p. 447–448 K, yield 34%). The crystal used for crystallographic analysis was grown in water.

Crystal data

$C_9H_{12}N_4O$
M_r = 192.22
Monoclinic
$P2_1/n$
a = 7.9572 (16) Å
b = 15.7497 (12) Å
c = 8.5050 (15) Å
β = 110.197 (21)°
V = 1000.3 (3) Å^3
Z = 4
D_x = 1.28 Mg m^{-3}
Mo $K\alpha$ radiation
λ = 0.7107 Å
Cell parameters from 24 reflections
θ = 1–22.5°
μ = 0.08 mm^{-1}
T = 290 K
Needle
0.30 × 0.20 × 0.10 mm
Yellow

Data collection

Enraf–Nonius CAD-4/PC diffractometer
$\omega/2\theta$ scans
Absorption correction: ψ scans (North, Phillips & Mathews, 1968)
T_{min} = 0.851, T_{max} = 0.998
1405 measured reflections
1307 independent reflections
706 observed reflections [$I > 2.5\sigma(I)$]
R_{int} = 0.047
θ_{max} = 22.5°
$h = -8 \rightarrow 8$
$k = 0 \rightarrow 16$
$l = 0 \rightarrow 9$
3 standard reflections
frequency: 60 min
intensity decay: 2%

Refinement

Refinement on F
R = 0.061
wR = 0.050
S = 3.43
706 reflections
$w = 1/[\sigma^2(F) + 5.0 \times 10^{-6}F^2]$
$(\Delta/\sigma)_{max} < 0.001$
$\Delta\rho_{max}$ = 0.21 e Å^{-3}
$\Delta\rho_{min}$ = −0.22 e Å^{-3}

127 parameters
H-atom parameters obtained from difference map and not refined
Atomic scattering factors from *International Tables for X-ray Crystallography* (1974, Vol. IV)

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

$$B_{eq} = (8\pi^2/3)\Sigma_i\Sigma_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j.$$

	x	y	z	B_{eq}
O	0.5649 (5)	0.1874 (3)	0.9878 (5)	5.0 (3)
N1	0.7836 (6)	0.2628 (3)	1.1743 (6)	4.3 (3)
N2	0.7359 (7)	−0.0834 (3)	1.5767 (7)	4.1 (3)
N3	0.8149 (7)	−0.0679 (3)	1.7329 (7)	4.8 (3)
N4	0.8235 (7)	−0.1328 (3)	1.8319 (7)	5.1 (4)
C1	0.7012 (8)	0.1236 (4)	1.2536 (7)	3.4 (3)
C2	0.5933 (8)	0.0532 (4)	1.2050 (7)	4.0 (4)
C3	0.6072 (8)	−0.0146 (4)	1.3125 (8)	4.4 (4)
C4	0.7307 (8)	−0.0103 (4)	1.4747 (7)	3.4 (4)
C5	0.8394 (8)	0.0600 (4)	1.5266 (7)	3.7 (4)
C6	0.8278 (8)	0.1267 (4)	1.4177 (7)	3.9 (4)
C7	0.6789 (8)	0.1936 (4)	1.1287 (8)	3.9 (4)
C8	0.9029 (10)	−0.1171 (4)	2.0130 (9)	7.2 (5)
C9	0.7426 (9)	−0.2156 (4)	1.7716 (8)	5.7 (4)

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

O—C7	1.232 (7)	C1—C2	1.376 (9)
N1—C7	1.345 (8)	C1—C6	1.412 (8)
N2—N3	1.282 (8)	C1—C7	1.498 (8)
N2—C4	1.433 (8)	C2—C3	1.385 (9)
N3—N4	1.312 (8)	C3—C4	1.392 (8)
N4—C8	1.470 (9)	C4—C5	1.380 (9)
N4—C9	1.466 (8)	C5—C6	1.383 (9)
N3—N2—C4	112.1 (5)	C2—C3—C4	119.0 (6)
N2—N3—N4	114.6 (5)	N2—C4—C3	115.1 (6)
N3—N4—C8	116.7 (5)	N2—C4—C5	124.5 (5)
N3—N4—C9	123.4 (5)	C3—C4—C5	120.4 (6)
C8—N4—C9	119.6 (5)	C4—C5—C6	120.3 (5)
C2—C1—C6	118.9 (5)	C1—C6—C5	119.8 (5)
C2—C1—C7	118.1 (5)	O—C7—N1	121.3 (6)
C6—C1—C7	123.0 (6)	O—C7—C1	120.0 (6)
C1—C2—C3	121.6 (5)	N1—C7—C1	118.8 (5)

D—H···*A*	H···*A*	*D*···*A*	*D*—H···*A*
N1—HN1*A*···O^{i}	1.93	2.935 (6)	150
N1—HN1*B*···N2^{ii}	2.10	3.197 (7)	169

Symmetry codes: (i) $\frac{1}{2}+x, \frac{1}{2}-y, \frac{1}{2}+z$; (ii) $\frac{3}{2}-x, \frac{1}{2}+y, \frac{5}{2}-z$.

Table 3. *Comparison of bond lengths* (Å) *of selected triazenes*

	(2)	(3)[a]	(4)[b]	(5)[c]	(6)[a]	(7)[d]
C4—N2	1.433 (8)	1.415 (2)	1.418 (1)	1.422 (3)	1.48 (2)	1.429 (8)
N2—N3	1.282 (8)	1.282 (2)	1.270 (1)	1.275 (3)	1.29 (2)	1.281 (7)
N3—N4	1.312 (8)	1.307 (2)	1.316 (1)	1.319 (3)	1.344 (15)	1.309 (7)
N4—C8	1.470 (9)	1.454 (2)	1.445 (2)	1.451 (4)	1.46 (2)	1.45 (1)

References: (*a*) Neidle & Wilman (1992); (*b*) Fronczek, Hansch & Watkins (1988); (*c*) Randall, Schwalbe & Vaughan (1984); (*d*) Edwards, Chapuis, Templeton & Zalkin (1977).

All crystallographic calculations were conducted with the PC version of the *NRCVAX* program package (Gabe, Le Page, Charland, Lee & White, 1989) locally implemented on an IBM compatible 80486 computer.

Lists of structure factors, anisotropic displacement parameters, H-atom coordinates and complete geometry have been deposited with the IUCr (Reference: FG1045). Copies may be obtained through The Managing Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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Ondansetron Hydrochloride: a Competitive Serotonin 5-HT$_3$ Receptor Blocker

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Abstract

The methyl substituted imidazole ring in the title compound, 2-methyl-1-(9-methyl-4-oxo-2,3,4,9-tetrahydro-1*H*-carbazol-3-yl)imidazol-3-ium chloride dihydrate, $C_{18}H_{20}N_3O^+.Cl^-.2H_2O$, is approximately perpendicular to the carbazole plane [dihedral angle 87.0 (1)°]. The water molecules are involved in an elaborate network of hydrogen bonds that reinforce the stability of the dihydrate and the cohesion of the structure.