thiodeacylaprophen may be due to its short $\mathrm{S}\cdots\mathrm{N}^+$ distance, the more shielded nature of its S atom relative to the carbonyl O atom of aprophen, the differing position of the N^+—H group, and the greater hydrophobicity of a thioether group *versus* an ester group since these features constitute the major structural and chemical differences between thiodeacylaprophen and aprophen. Since thiodeacylaprophen is selective for the muscarinic receptor subtype found in pancreatic tissue, the three-dimensional structure of thiodeacylaprophen should aid modeling the structure of muscarinic receptor subtypes and modeling the interaction of antimuscarinic agents with the muscarinic receptor subtypes.

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X-ray Studies on Anti-Tumour Triazenes. Structures of 1-(4-Carbamoylphenyl)-3,3-dimethyltriazene 1-Oxide and 3,3-Dimethyl-1-(4-nitrophenyl)triazene

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Abstract

The molecular structures of the title compounds have been determined by X-ray crystallographic methods. The analyses revealed differences in the geometry, and by inference the bond delocalization in these two triazenes owing to the presence in the 1-oxide structure of an N—O bond. The geometries are compared to the crystal structures of the isomeric 3-oxides [Kuroda & Wilman (1985). *Acta Cryst.* **C41**, 1543–1545; Neidle, Webster, Kuroda & Wilman (1987).

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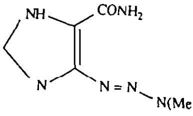
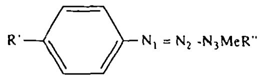
Acta Cryst. C**43**, 674–676] which shows the dominance of an alternative tautomeric equilibrium for the triazene groups.

Introduction

The triazene compound DTIC [(1), 5-(3,3-dimethyltriazen-1-yl)imidazole-4-carboxamide] has clinically useful anti-tumour activity. It is the single most effective agent in the treatment of malignant melanoma (Miles & Souhami, 1987) and has demonstrated activity against Hodgkin's disease (Bonadonna, Uslenghi & Zucali, 1975) and soft tissue sarcoma (Breithaupt, Dammann & Aigner, 1982). DTIC is myelo-suppressive, and its use in combination therapy has been further limited by its short half-life (Connors, Goddard, Merai, Ross & Wilman, 1976). Aryltriazenes are synthetically more accessible, and have been extensively studied in a search for second-generation anti-tumour triazenes with enhanced stability and activity. In general, activity in these series is associated with the possession of a methyl group at the nitrogen N3 position (2) (Wilman, Cox, Goddard, Hart, Merai & Newell, 1984; Wilman, 1985) together with a readily metabolized group *R''*. The phenyl group at the N1 position is effectively a carrying group. Their anti-tumour activity is believed to depend on oxidative metabolism mechanisms (Connors, Goddard, Merai, Ross & Wilman, 1976; Gescher, Hickman, Simmonds, Stevens & Vaughan, 1978) as well as partial dealkylation pathways (Vaughan, Tang, Llanos, Horton, Simmonds, Hickman & Stevens, 1984).

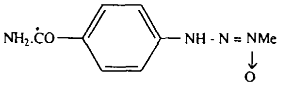


(1)

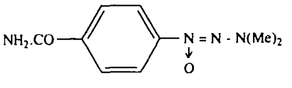


(2)

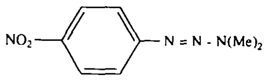
In the course of these studies a number of *N*-oxides have been examined. Although they might be considered to have involvement in triazene metabolism, at present there is no direct evidence for this. The 3-(4-carbamoylphenyl)-1-methyltriazene 1-oxide (3) (Connors, Goddard, Merai, Ross & Wilman, 1976) has activity against the TLX5 lymphoma and the adj PC6/A plasmacytoma (Wilman, 1985), whereas its methoxy analogue 1-(4-carbamoylphenyl)-3-methoxy-3-methyltriazene is devoid of activity. These differences may be ascribable to differences in their susceptibility to metabolic attack at N3 so as to proceed to a monomethyltriazene. Compound (3) is a true *N*-oxide with N3 being electron deficient rather than the tautomeric *N*-hydroxyl form, as shown by NMR (Guimanini, Lassiani, Nisi, Petric & Stanovnik, 1983) and X-ray crystallographic studies (Kuroda & Wilman, 1985). Compound (3) is of especial interest in that it has superior stability properties to those of DTIC itself, and has alternative metabolic requirements for formation of the active monomethyltriazene metabolite.



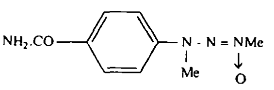
(3)



(4)



(5)



(6)

The present study reports on structural aspects of the 1-oxide (4) which has shown anti-tumour activity (Wilman & Goddard, 1991). Structual details are also reported here for a parent dimethyltriazene (5), since little data on these is available in the literature, and it provides a point of comparison for the various triazene 1-oxides. The structure of the 3-methyl derivative of (3), *i.e.* compound (6), has been reported previously by Neidle, Webster, Kuroda & Wilman (1987).

Experimental

1-(4-Carbamoylphenyl)-3,3-dimethyltriazene 1-oxide (4) was synthesized as reported elsewhere (Wilman & Goddard, 1991). 3,3-Dimethyl-1-(4-nitrophenyl)triazene (5) was prepared according to the method of Elks & Hey (1943).

Both compounds (4) and (5) were recrystallized from benzene solution as colourless elongated prisms. These had a tendency to multiply twin. Preliminary crystal data were obtained on oscillation and Weissenberg cameras. Accurate cell dimensions were obtained by least-squares refinements of 25 reflections in the range $1.5 \leq \theta \leq 30°$ measured on an Enraf–Nonius CAD-4 diffractometer (Table 1). Intensity data were collected on the diffractometer with ω–2θ scans and Ni-filtered Cu $K\alpha$ radiation (λ = 1.54178 Å). In each case, periodic checks on three strong reflections did not show any significant decay. The structures were solved by direct methods using the *MULTAN*11/82 program (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1982). Refinements were by means of a full-matrix least-squares technique with non-H atoms being assigned individual anisotropic temperature factors and with refinement of F values. In the case of (4) the relatively small number of observed reflections precluded refinement of H-atom positional and thermal parameters. They were kept at calculated positions with assigned temperature factors of 5.0 Å^2. In the case of

Table 1. *Crystallographic data*

	(4)	(5)
Empirical formula	$C_9H_{12}N_4O_2$	$C_8H_{10}N_4O_2$
M_r	208.2	194.2
Symmetry	Monoclinic	Triclinic
Space group	$P2_1/c$	$P\bar{1}$
a (Å)	4.933 (2)	5.966 (1)
b (Å)	9.409 (1)	7.681 (1)
c (Å)	22.865 (4)	10.483 (1)
α (°)	90.00	103.29 (1)
β (°)	94.16 (2)	93.08 (1)
γ (°)	90.00	94.61 (1)
V (Å^3)	1058.5 (5)	464.7 (1)
Z	4	2
D_x (g cm^{-3})	1.312	1.388
μ (cm^{-1})	7.65	8.31
F(000)	440.0	204.0
T (K)	298	298
Crystal size (mm)	0.2 × 0.15 × 0.3	0.25 × 0.15 × 0.4
No. of reflections measured (unique set only)	1336	1763
hkl range	$0 < h < 5$ $0 < k \leq 9$ $-21 \leq l \leq 21$	$0 < h \leq 7$ $-9 \leq k \leq 9$ $-13 \leq l \leq 13$
θ range (°)	1.5–55.0	1.5–70.0
Maximum scan time (s)	150	90
No. of reflections with $I > 3\sigma(I)$	513	1313
R	0.097	0.063
wR	0.116	0.074
Maximum Δ/σ	0.03	0.0
Maximum/minimum $\Delta\rho$ (e Å^{-3})	0.3/−0.2	0.2/−0.1
Absorption correction transmission coefficients T_{min}/T_{max}	0.92/1.10	0.91/1.14

(5) all H atoms, except those in methyl groups, had their positional parameters refined. All H-atom temperature factors were fixed at 5.0 Å^2. Empirical absorption corrections were applied to both structures (Walker & Stuart, 1983). Weights used were of the form $1/[\sigma^2(F_o) + 0.04|F_o|^2]$. All calculations were performed with the Enraf–Nonius *SDP* package (Frenz, 1981) on a VAX 11/750 computer.* Atomic scattering factors were from *International Tables for X-ray Crystallography* (1974, Vol. IV).

Results and discussion

The molecular structure of the triazene 1-oxide (4) is shown in Fig. 1; Tables 2 and 3 detail non-H-atom positional parameters and molecular geometry. The poor quality and small size of the crystal used resulted in large e.s.d.'s for the geometric parameters, so a very detailed comparison with other structures is not possible. The N2—N3 bond is significantly longer than the N1—N2 bond [by 0.15 (2) Å], and is in agreement with the tautomerism shown in (4) (Table 3). This situation is the reverse of that found in the two triazene 3-oxides (2) and (3) (Kuroda & Wilman, 1985; Neidle, Webster, Kuroda & Wilman, 1987). The O1—N1 distance of 1.28 (2) Å in (4) is significantly longer than a pure N═O double bond, suggesting that the tautomer represented by (4) is the dominant form observed. The four atoms of the triazene *N*-oxide group in (4) are closely coplanar (χ^2 = 2); the least-squares plane of this group is inclined at an angle of 13 (1)° to that of the phenyl group (Fig. 1). The C2—C1—N1—O1 torsion angle is 17 (1)°. This non-coplanarity is probably a consequence of steric hindrance between atoms O1 and H2, and results in a slight though significant decrease in overall delocalization, as evidenced by the C1—N1 bond length of 1.48 (2) Å being significantly longer than in the other benzylidene–triazene structures (3), (5) and (6). Substitution at the N1 position of a 1,3,3-trisubstituted triazene would in principle result in geometric isomerism about the N1—N2 bond. In the structure of (4), the O atom and the N3 dimethyl group are *cis* to each other. The angles round atom N1 are non-equivalent; the O1—N1—N2 angle of 130 (1)° may result from the relief of the steric hindrance between O1 and a methyl group. The four atoms of the amide groups in (4) are highly coplanar, with a χ^2 value of zero and an O2—C7—N4—N4 torsion angle of 9 (2)°. The group as a whole is non-coplanar with the phenyl ring [interplane angle of 30 (1)° and N4—C7—C4—C3 torsion angle of 29 (1)°]. This is probably ascribable to relief of steric clashes between H atoms on N4 and C3: their non-bonded separation in the structure is 2.01 (2) Å, whereas with coplanarity of the amide and phenyl groups this would be reduced to 1.77 Å. Energy calculations indicate that this would increase the non-bonded energy of the molecule by about 4 kcal mol^{-1}* (S. Neidle, unpublished observations).

The molecular structure of the nitrophenyltriazene (5) is shown in Fig. 2. The *transoid* arrangement generally found in the aryltriazenes is observed

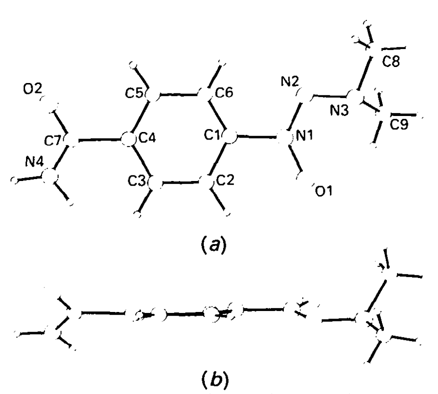


Fig. 1. Two computer-drawn views of the molecular structure of compound (4): (*a*) projected onto the mean plane of the phenyl ring; (*b*) perpendicular to this plane.

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* Lists of structure factors, anisotropic thermal parameters and H-atom positions have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 54728 (20 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: LI0113]

* 1 kcal mol^{-1} = 4.184 kJ mol^{-1}.

Table 2. *Positional parameters and averaged equivalent isotropic temperature factors* (Å^2) *for the non*-H *atoms in* (4) *and* (5), *with e.s.d.'s in parentheses*

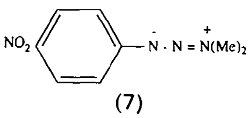
$$B_{eq} = 8\pi^2(U_{11}U_{22}U_{33})^{1/3}.$$

	x	y	z	B_{eq}
(4)				
O1	1.256 (2)	−0.122 (1)	0.1380 (4)	6.4 (3)
O2	1.240 (2)	0.065 (1)	0.4435 (5)	6.7 (3)
N3	0.943 (2)	0.068 (1)	0.0824 (5)	5.1 (3)
N2	0.999 (2)	0.086 (1)	0.1403 (4)	4.7 (3)
N1	1.150 (2)	−0.015 (1)	0.1629 (5)	5.3 (3)
N4	1.669 (2)	0.005 (1)	0.4288 (4)	3.9 (3)
C1	1.211 (3)	0.000 (1)	0.2271 (6)	4.4 (4)
C2	1.434 (3)	−0.080 (2)	0.2505 (6)	5.3 (4)
C3	1.505 (3)	−0.067 (2)	0.3097 (7)	6.1 (4)
C4	1.361 (2)	0.023 (1)	0.3437 (6)	3.8 (3)
C5	1.160 (3)	0.108 (1)	0.3184 (6)	4.4 (4)
C6	1.097 (3)	0.097 (1)	0.2572 (6)	4.7 (4)
C7	1.430 (2)	0.031 (2)	0.4110 (6)	3.9 (3)
C8	0.790 (4)	0.192 (2)	0.0614 (8)	9.5 (6)
C9	0.812 (3)	−0.064 (2)	0.0604 (7)	6.3 (4)
(5)				
O1	1.3771 (4)	0.5123 (4)	1.2255 (3)	6.24 (7)
O2	1.0481 (5)	0.4880 (4)	1.2976 (2)	5.97 (7)
N1	0.8725 (4)	0.0022 (3)	0.7195 (2)	3.23 (5)
N2	0.6610 (4)	−0.0497 (3)	0.7047 (2)	3.20 (5)
N3	0.5949 (4)	−0.1584 (3)	0.5912 (2)	3.33 (5)
N4	1.1791 (5)	0.4540 (3)	1.2109 (2)	3.85 (6)
C1	0.9337 (5)	0.1167 (3)	0.8448 (2)	2.77 (5)
C2	0.7929 (5)	0.1522 (4)	0.9482 (3)	3.34 (6)
C3	0.8708 (5)	0.2634 (4)	1.0671 (3)	3.54 (6)
C4	1.0933 (5)	0.3382 (3)	1.0842 (2)	2.88 (5)
C5	1.2349 (5)	0.3047 (4)	0.9841 (3)	3.38 (6)
C6	1.1551 (5)	0.1950 (4)	0.8655 (3)	3.41 (6)
C8	0.3622 (6)	−0.2303 (5)	0.5740 (3)	4.77 (8)
C9	0.7529 (6)	−0.2236 (5)	0.4944 (3)	4.26 (7)

Table 3. *Bond lengths* (Å) *and angles* (°) *in aryltriazenes for the triazene moiety and its substituents, with e.s.d.'s in parentheses*

	(3)	(4)	(5)	(6)
C1—N1	1.403 (2)	1.48 (2)	1.415 (2)	1.405 (2)
N1—CMe	-	-	-	1.473 (3)
N1—O1	-	1.28 (2)	-	-
N1—H1	1.05 (3)	-	-	-
N1—N2	1.340 (3)	1.29 (2)	1.282 (2)	1.383 (2)
N2—N3	1.271 (3)	1.344 (15)	1.307 (2)	1.280 (2)
N3—C8	1.464 (4)	1.45 (2)	1.438 (2)	1.470 (3)
N3—C9	-	1.47 (2)	1.454 (2)	-
N3—O3	1.284 (3)	-	-	1.209 (2)
C1—N1—N2	118.2 (2)	114 (1)	111.6 (1)	112.9 (2)
C1—N1—O1	-	117 (1)	-	-
O1—N1—N2	-	130 (1)	-	-
C1—N1—CMe	-	-	-	118.5 (2)
N2—N1—CMe	-	-	-	116.5 (2)
N1—N2—N3	112.1 (2)	112 (1)	114.5 (1)	112.3 (2)
N2—N3—C8	116.9 (2)	107 (1)	116.4 (1)	114.6 (2)
N2—N3—C9	-	120 (1)	122.1 (1)	-
C8—N3—C9	-	111 (1)	121.0 (1)	-
N2—N3—O3	124.1 (2)	-	-	127.6 (2)
C8—N3—O3	119.0 (2)	-	-	117.8 (2)

in this structure. By contrast with the *N*-oxides (3), (4) and (6), the two N—N bond lengths (N1—N2 and N2—N3) differ by only 0.025 Å (10σ). This smaller difference has been observed for N1—N2 and N2—N3 bonds in 3-methyl-1-*p*-tolyltriazene with lengths of 1.275 (3) and 1.319 (3) Å (Randall, Schwalbe & Vaughan, 1984), in DTIC with lengths of 1.288 (3) and 1.305 (3) Å (Edwards, Sherfinski & Marsh, 1974), in 2-(3,3-dimethyl-1-triazeno)benzamide with lengths of 1.281 (7) and 1.309 (7) Å (Edwards, Chapuis, Templeton & Zalkin, 1977), and in *p*-(3,3-dimethyl-1-triazeno)benzonitrile with lengths of 1.270 (1) and 1.316 (1) Å (Fronczek, Hansch & Watkins, 1988). It appears that the N1—N2—N3 triazene group is significantly delocalized in these compounds and that there is a significant contribution of tautomer (7) to the overall structure, as evidenced from the *sp*^{2}-like angles around N3. It also suggests that the N1—N2 and N2—N3 distances are not especially sensitive to differences in aryl substituents at, in particular N1. An MNDO molecular orbital study (Ramos & Pereia, 1986) of (5) on the other hand, calculated N1—N2 and N2—N3 distances of 1.245 and 1.319 Å with a conformation favouring an intramolecular interaction between N1 and one of the terminal methyl groups. These features have not been observed in the crystal structures of triazenes, including (5), and suggest that such semi-empirical quantum calculations may not adequately describe these compounds.



(7)

The triazene group in (5) is inclined at a dihedral angle of 7.3 (2)° to the phenyl ring, and the nitro group at the other end of the molecule is at an angle of 3.0 (2)° to the ring, consistent in both cases with extensive delocalization. The C1—N1 bond length in (5) is shortened by 0.065 Å compared with that in (4), which is also consistent with triazene–phenyl conjugation. It has been noted previously that overall coplanarity of aromatic triazenes, as found in compound (5) and 3-methyl-1-*p*-tolyltriazene (Randall, Schwalbe & Vaughan, 1984), is not dependent on hydrogen-bonding factors, as found in the structure of DTIC (Edwards, Sherfinski & Marsh, 1974). This conclusion is also borne out by the present study.

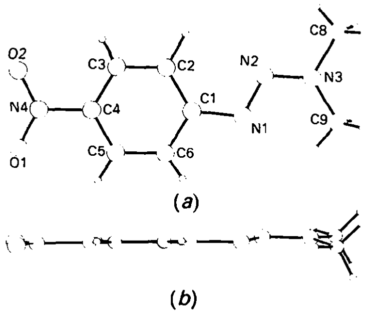


Fig. 2. Two computer-drawn views of the molecular structure of compound (5). Projections (*a*) and (*b*) as in Fig. 1.

The observed non-equivalence (by 7σ) between the two terminal N3—C lengths in (5) is unexpected and not readily explicable. It is tempting to speculate that this implies differences in reactivity and to the oxidative metabolism of triazenes that occurs at just one of these two methyl groups. The crystal structures of further dimethyltriazenes should serve to illuminate this issue.

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Electrostatic Properties of 1-Methyluracil from Diffraction Data

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Abstract

1-Methyluracil (1-methyl-2,4-dioxopyrimidine), $C_5H_6N_2O_2$, $M_r = 126.12$, orthorhombic, *Ibam*, $a = 13.188\,(6)$, $b = 13.175\,(5)$, $c = 6.214\,(3)$ Å, $V = 1079.7\,(8)$ Å^3, $Z = 8$, $D_x = 1.552$ g cm^{-3}, $\lambda(\text{Mo }K\alpha) = 0.7107$ Å, $\mu = 1.317$ cm^{-1}, $F(000) = 528$, $T = 123$ K, $R(F^2) = 0.068$ for 2996 reflections with $\sin\theta/\lambda < 1.08$ Å^{-1}. The electronic charge-density distribution has been analyzed in terms of Stewart's rigid pseudoatom model, using restricted Slater radial functions and angular multipole terms extending to octapoles for C, N and O, and quadrupoles for H pseudoatoms. Three different structure refinements have been carried out based on two X-ray diffraction data sets from different crystals collected at temperatures differing by about 20 K. The molecular dipole moment is 6.4 (27) D. Maps of the electrostatic potential for a molecule isolated from the crystal show that atoms O2 and O4 confer overall electronegativity on one side of the molecule while the CH groups and the C1 methyl group confer electropositivity on the other. For the centrosymmetric hydrogen-bonded dimer (N3—H3$\cdots$O4'; H$\cdots$O distances 1.77 Å) the electrostatic potential shows electropositive bridges between the molecules. These features are lacking for the C—H$\cdots$O interactions (distances H6$\cdots$O2, 2.37; H11$\cdots$O4, 2.34 Å). The electron density and its Laplacian have been determined at the intramolecular bond-critical points and also for the intermolecular H$\cdots$O interactions. Values for the former are characteristic of covalent bonds. Values of the electron density and Laplacian for the C—H$\cdots$O interactions are very small and have little

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