Acta Cryst. (1979). B35, 2051–2054

The Crystal Structure of the Anti-Tumor Agent 5-(3,3-Dimethyl-1-triazenyl)imidazole-4-carboxamide (NSC-45388)

BY HANS C. FREEMAN AND NEIL D. HUTCHINSON

Department of Inorganic Chemistry, University of Sydney, Sydney 2006, *Australia*

(*Received* 14 *December* 1978; *accepted* 2 *May* 1979)

Abstract

The crystal structure of 5-(3,3-dimethyl-1-triazenyl)-imidazole-4-carboxamide (NSC-45388) has been determined from three-dimensional X-ray data. The crystals are monoclinic, space group $P2_1/n$, with a = 14·042 (2), b = 10·661 (2), c = 11·914 (4) Å, β = 91·49 (8)°, V = 1783·0 (8) Å^3, Z = 8. The structure was solved by direct methods and refined using block-diagonal least-squares calculations. The final R for 1350 independent observed reflections is 0·042. There are two molecules in the asymmetric unit. In one molecule the protonated N in the imidazole ring is adjacent to the triazene group, and in the other it is adjacent to the carboxamide group. Each molecule is approximately planar and contains an internal N—H···N hydrogen bond. Intermolecular hydrogen bonding produces sheets of molecules lying approximately perpendicular to the b axis.

Introduction

The title compound (DTIC) is used in the chemotherapy for malignant melanoma. The structure of the cation $HDTIC^+$ in crystals grown at very low pH has been determined by Edwards, Sherfinski & Marsh (1974). We now report the structure of neutral DTIC, as part of a study of the drug and its interactions with transition-metal ions (Freeman & Hutchinson, 1979).

Experimental

A crystal exhibiting the forms {100} and {011}, with dimensions 0·30 × 0·12 × 0·12 mm, was selected from a sample of DTIC supplied by the Drug Development Branch, National Cancer Institute, Bethesda, Maryland. Diffraction data were recorded on an Enraf–Nonius CAD-4/F automatic diffractometer using graphite-monochromated Mo $K\alpha$ radiation [λ(Mo $K\alpha_1$) = 0·70926, λ(Mo $K\alpha_2$) = 0·71354 Å]. The 2θ angle of the monochromator was 12·18° and the crystal-to-detector distance was 173 mm. Unit-cell dimensions were obtained by least-squares refinement of 2θ values for 23 automatically centered reflections ($\theta > 17°$).

Crystal data

Molecular formula $C_6H_{10}N_6O$, M_r = 182·20, monoclinic, a = 14·042 (2), b = 10·661 (2), c = 11·914 (4) Å, β = 91·49 (8)°, V = 1783·0 (8) Å^3; space group $P2_1/n$ from systematic absences ($h0l$ absent for $h + l$ odd, $0k0$ absent for k odd). D_x = 1·357 Mg m^{-3} for Z = 8 (2 molecules per asymmetric unit).

Profile analysis of a representative reflection indicated that the conditions for the measurement of integrated intensities would be optimized by ω–(S) 2θ scans, where $S = \frac{1}{2}$. The ω-scan angle and the horizontal counter aperture, both reduced as much as possible so as to minimize the effect of thermal diffuse scattering (Burbank, 1964), were (1·5 + 0·35 tan θ)° and (1·8 + 0·35 tan θ) mm, respectively. The scan speeds were determined by a required precision $\sigma(I) < 0{\cdot}005I$, subject to a maximum scan time of 180 s per reflection. Each reflection was scanned in 96 steps. The peak count P was recorded over the central 64 steps, with 16 steps at each end to measure the backgrounds B_1 and B_2. The intensity I was calculated as $I = v[P - 2(B_1 + B_2)]$ with standard deviation $\sigma(I) = \{v[P + 4(B_1 + B_2)]\}^{1/2}$, where v is a factor to account for the differences in scan speeds.

Three reference reflections were measured after every 250 min of X-ray exposure. The orientation of the crystal was checked after every 200 reflections. No decomposition or movement of the crystal was detected. Intensities were recorded for 2183 (hkl) reflections and 1655 equivalent ($h\bar{k}l$) reflections ($\theta < 22°$).

The data were corrected for the Lorentz and polarization factors. Absorption corrections were not applied (μ = 0·110 mm^{-1}). There were 732 pairs of equivalent reflections with $I > 3\sigma(I)$. The unweighted discrepancy factor R_D, defined as $(\sum |\Delta F|^2/\sum |F_{av}|^2)^{1/2}$, was 0·027, where $\Delta F = |F(hkl)| - |F(h\bar{k}l)|$ and $F_{av} = [|F(hkl)| + |F(h\bar{k}l)|]/2$.

An analysis of the errors in the data was made by dividing the data into 22 ranges of $|F_{av}|$ and plotting the mean $[(\Delta F)^2 - \sigma^2_{stat}(F)]$ values *versus* the mean

0567-7408/79/092051-04$01.00

$|F_{av}|$ values. Here $\sigma^2_{stat}(F)$ was the variance of an observed structure factor from counting statistics alone. The function $V_s(F) = l + m|F| + n|F|^2 + p|F|^3$, representing the contributions of systematic errors to the variances (Freeman & Guss, 1972), was fitted to the above plot. The coefficients were $l = -1{\cdot}69 \times 10^{-1}$, $m = 3{\cdot}86 \times 10^{-2}$, $n = 1{\cdot}14 \times 10^{-3}$, and $p = 9 \times 10^{-6}$. (By coincidence, these coefficients were on an approximately absolute scale. The factor subsequently required to convert the arbitrary F's to an absolute scale was 1·057.) A new variance $\sigma^2(F)$ for each reflection was calculated as the sum of $\sigma^2_{stat}(F)$ and $V_s(F)$. The data were then reduced to a single list of 2183 F values by averaging $F(hkl)$ and $F(\bar{h}\bar{k}\bar{l})$ whenever both had been measured. There were 833 F values derived from intensities $I < 3\sigma(I)$. The remaining 1350 values were used in the structure analysis.

Structure determination and refinement

The structure was solved by means of the direct-methods program package *MULTAN* (Germain, Main & Woolfson, 1971). The starting data were the 400 reflections with $|E| > 1{\cdot}3$. The set of phases with the highest figure of merit led to an E map in which all the non-hydrogen atoms could be located. Scattering factors for O, N, C and H were taken from *International Tables for X-ray Crystallography* (1974). Initially the structure was refined by full-matrix least-squares calculations. The function minimized was $\sum w(|F_o| - s|F_c|)^2$ where $w = \sigma^{-2}(F)$ and s is a scale factor. After several cycles of refinement in which the non-hydrogen atoms had anisotropic thermal parameters, the H atoms were located in an $(F_o - F_c)$ synthesis. In the final refinement cycles, the H atoms were included but were given a fixed thermal parameter ($U_{iso} = 0{\cdot}059$ Å^2). At this stage the matrix was partitioned into two blocks each containing the parameters for one molecule of the asymmetric unit. A final difference Fourier synthesis showed no peaks larger than 0·30 e Å^{-3}. The final residuals were $R\ (= \sum ||F_o| - s|F_c|| / \sum |F_o|) = 0{\cdot}042$ and $R_w\ \{= [\sum w(|F_o| - s|F_c|)^2 / \sum w|F_o|^2]^{1/2}\} = 0{\cdot}030$ for the 1350 reflections used in the refinement. The atomic positional parameters are shown in Table 1.*

Table 1. *Positional parameters (fractional coordinates* $\times 10^4$*) with estimated standard deviations in parentheses*

	x	y	z
C(1)	8337 (2)	8195 (3)	3686 (3)
C(2)	9003 (2)	8602 (3)	5331 (2)
C(3)	9689 (2)	8263 (3)	4581 (2)
C(4)	10724 (2)	8120 (3)	4750 (3)
C(5)	9470 (3)	9668 (4)	8496 (3)
C(6)	7695 (3)	10018 (5)	8562 (4)
C(7)	6009 (2)	8072 (3)	6451 (3)
C(8)	5379 (2)	8474 (3)	4842 (2)
C(9)	4652 (2)	8151 (3)	5530 (2)
C(10)	3609 (2)	8055 (3)	5358 (3)
C(11)	4978 (3)	9451 (5)	1618 (3)
C(12)	6740 (3)	9858 (4)	1628 (4)
N(1)	9264 (2)	8007 (2)	3542 (2)
N(2)	8147 (2)	8555 (3)	4745 (2)
N(3)	11065 (2)	8417 (3)	5775 (3)
N(4)	9159 (2)	8953 (2)	6438 (2)
N(5)	8391 (2)	9285 (3)	6921 (2)
N(6)	8532 (2)	9651 (3)	7956 (2)
N(7)	5073 (2)	7894 (2)	6563 (2)
N(8)	6238 (2)	8428 (2)	5424 (2)
N(9)	3281 (2)	8296 (3)	4329 (2)
N(10)	5235 (2)	8808 (2)	3720 (2)
N(11)	6013 (2)	9130 (2)	3252 (2)
N(12)	5891 (2)	9466 (3)	2201 (2)
O(1)	11228 (1)	7742 (2)	3992 (2)
O(2)	3098 (1)	7745 (2)	6139 (2)
H(1)	7859 (20)	8045 (28)	3036 (24)
H(2)	7576 (20)	8593 (29)	5069 (28)
H(3)	10606 (22)	8821 (26)	6393 (24)
H(4)	11567 (23)	8339 (34)	5886 (28)
H(5)	9769 (23)	8903 (29)	8439 (27)
H(6)	9963 (20)	10081 (28)	7937 (26)
H(7)	9364 (20)	10089 (29)	9199 (26)
H(8)	7803 (22)	10691 (32)	8967 (27)
H(9)	7546 (22)	9402 (30)	9152 (25)
H(10)	7135 (21)	9978 (30)	8098 (26)
H(11)	6449 (20)	7928 (27)	7137 (25)
H(12)	4784 (22)	7601 (30)	7206 (24)
H(13)	3616 (23)	8585 (30)	3842 (26)
H(14)	2654 (21)	8250 (30)	4157 (26)
H(15)	4583 (23)	8842 (30)	1869 (27)
H(16)	4546 (21)	10188 (29)	1957 (26)
H(17)	5092 (22)	9522 (30)	890 (24)
H(18)	6572 (22)	10435 (32)	1132 (27)
H(19)	6912 (22)	9230 (30)	1073 (25)
H(20)	7234 (22)	10117 (30)	2151 (27)

Description of the structure

The asymmetric unit consists of two non-identical molecules. Their dimensions are shown in Fig. 1. In molecule 1, a H atom (located by the structure analysis) is attached to the imidazole nitrogen N(2), adjacent to the triazene group. In molecule 2 the protonated imidazole nitrogen is N(7), adjacent to the carboxamide group. The formal nomenclature, in which the numbering starts at the imidazole N to which the H is attached, is 5-(3,3-dimethyl-1-triazenyl)-imidazole-4-carboxamide for molecule 1 and 4-(3,3-dimethyl-1-triazenyl)imidazole-5-carboxamide for molecule 2.

* Lists of structure factors, anisotropic thermal parameters and least-squares planes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 34438 (20 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

A comparison of the dimensions of molecules 1 and 2 in the orientations of Fig. 1 reveals a significant difference (4·5 times its own standard deviation) between the lengths of the bonds C(1)–N(2), 1·352 (4) Å, and C(7)–N(8), 1·328 (4) Å. In addition, every internal bond angle in the imidazole ring of molecule 1 except N(1)–C(1)–N(2) is significantly different from the internal angle at the corresponding atom of molecule 2. For example, in molecule 1 the internal angle at the ring C to which the triazene group is attached is 106°, and the internal angle at the C to which the carboxamide group is attached is 110°. In molecule 2 the values of these angles are interchanged (with concomitant changes in the bond angles which are external to the ring). The differences between pairs of corresponding dimensions in molecules 1 and 2 disappear if the 'corresponding' positions are defined not in relation to the substituents on the rings, but in relation to the protonated imidazole N atoms. The angles in the imidazole rings of both molecules then also become, within the limits of precision, consistent with those in crystalline imidazole (Craven, McMullen, Bell & Freeman, 1977). A similar dependence of the internal bond angles in imidazole rings on the position of the protonated N has been noted in 5-amino-4-carbamoyl-1*H*-imidazole and 4-amino-5-carbamoyl-1*H*-imidazole.H_2O (A. Kàlmàn, F. van Meurs & J. To'th, personal communication).

The sequences N(2)–C(2)–N(4)–N(5) and N(8)–C(8)–N(10)–N(11) are in *syn* configurations. There are intramolecular hydrogen bonds N(3)–H···N(4) (2·868 Å) and N(9)–H···N(10) (2·908 Å) between the carboxamide and triazene side chains. The imidazole rings and the carboxamide groups in both molecules are planar within the limits of precision.* The entire molecules, however, are not strictly planar. The bonds C(3)–C(4) and C(9)–C(10) are bent by 1·4 and 0·5°, respectively, from the imidazole planes. The carboxamide groups are rotated by 2·5 and 1·0°, respectively, about the C–C bonds. Further deviations from planarity are caused by out-of-plane bending of the bonds C(2)–N(4) (1·3°) and C(8)–N(10) (0·2°), and by small rotations about the C–N and N–N bonds within the triazene groups. The carboxamide and triazene groups are bent and rotated to *opposite* sides of the imidazole plane in molecule 1, and to the *same* side in molecule 2.

A similar molecular configuration, an equivalent intramolecular hydrogen bond (2·974 Å), and slightly greater deviations from planarity are found in the $HDTIC^+$ cation (Edwards *et al.*, 1974). Differences between the bond lengths in DTIC and $HDTIC^+$ are probably not significant, but a number of marked differences do occur between corresponding bond angles. In $HDTIC^+$ the internal bond angles of the imidazole ring are all close to 108°. In DTIC the angles at C(1) in molecule 1 and at C(7) in molecule 2 are 112–113°, and the angles at N(1), C(2), N(8) and C(9) are 104–106°. There are similar differences between the protonated and neutral forms of the imidazole rings in L-histidine (Madden, McGandy & Seeman, 1972) and also of imidazole itself (Freeman, Huq, Rosalky & Taylor, 1975).

The molecular packing in the crystals of DTIC bears no resemblance to that in $HDTIC^+Cl^-.H_2O$. Infinite DTIC chains in which molecules 1 and 2 alternate are formed by hydrogen bonds N(2)–H···N(8) and N(7)–H···N(1) between the imidazole rings (Fig. 2 and Table 2). The angle between the average planes of adjacent DTIC molecules in the chains is 36·3°.

* See deposition footnote.

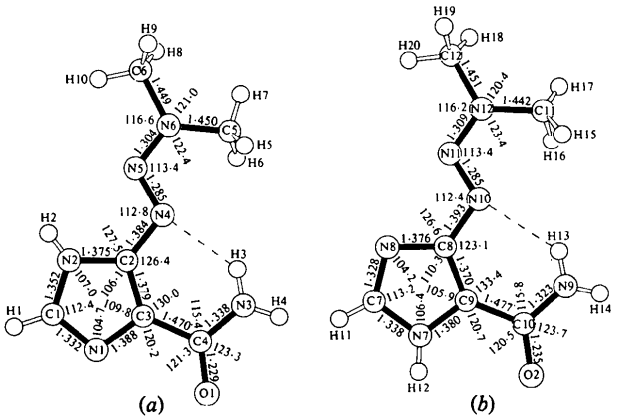

Fig. 1. Molecular geometry and dimensions [bond lengths (Å) and angles (°)] of DTIC, (*a*) molecule 1, (*b*) molecule 2. The estimated standard deviations of the bond distances and angles are 0·004 Å and 0·3°, respectively.

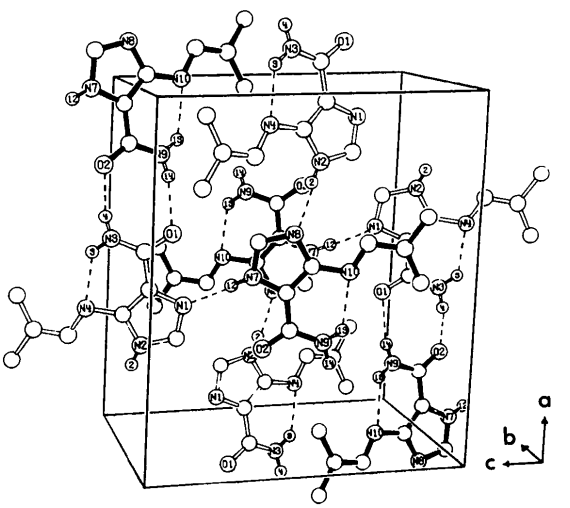

Fig. 2. Packing of DTIC molecules in relation to the unit cell. Molecules symmetry related to molecules 1 and 2 have hollow and filled bonds, respectively. Hydrogen bonds are shown as dashed lines.

Table 2. *Hydrogen bonding*

Superscripts refer to the following equivalent positions:

None	x, y, z	(iii)	$1+x, y, z$
(i)	$-\frac{1}{2}+x, 1\frac{1}{2}-y, \frac{1}{2}+z$	(iv)	$-1+x, y, z.$
(ii)	$\frac{1}{2}+x, 1\frac{1}{2}-y, -\frac{1}{2}+z$		

X–H···Y	X–Y (Å)	H···Y (Å)	∠X–H···Y (°)
N(2)–H(2)···N(8)	2·824 (4)	1·94 (3)	165 (3)
N(3)–H(3)···N(4)	2·868 (4)	2·04 (3)	131 (2)
N(3)–H(4)···O(2^{iii}) / N(3^{iv})–H(4^{iv})···O(2)	2·964 (3)	2·25 (3)	170 (4)
N(7)–H(12)···N(1^{i}) / N(7^{ii})–H(12^{ii})···N(1)	2·813 (4)	1·88 (3)	177 (3)
N(9)–H(13)···N(10)	2·908 (4)	2·29 (3)	132 (3)
N(9)–H(14)···O(1^{iv}) / N(9^{iii})–H(14^{iii})···O(1)	2·960 (3)	2·08 (3)	166 (3)

Similar strong hydrogen bonds occur in imidazole (Craven *et al.*, 1977) where the N–H···N distance is 2·86 Å compared with values of 2·83 and 2·81 Å in the present structure. Cross linking between the chains of DTIC molecules is provided by pairs of hydrogen bonds between amide groups [N(3)–H···O(2) and N(9)–H···O(1)]. In the directions normal to the planes of the imidazole rings there are no contacts shorter than 3·5 Å with neighboring molecules.

Results of the present work which may be relevant to the biological effects of DTIC are that (i) the side-chain configurations are not affected by changes in pH (since the same configurations are observed in crystals of DTIC and HDTIC$^+$ grown under quite different conditions and having different intermolecular interactions), and (ii) the shape of the imidazole ring undergoes subtle changes depending on whether one N(imidazole) atom or the other or both are protonated.

We thank Dr H. B. Wood of the National Cancer Institute, US Public Health Service, for a gift of DTIC, and the Australian Research Grants Committee for financial support (Grant 74/15398).

References

BURBANK, R. D. (1964). *Acta Cryst.* **17**, 434–442.
CRAVEN, B. M., MCMULLEN, R. K., BELL, J. D. & FREEMAN, H. C. (1977). *Acta Cryst.* B**33**, 2585–2589.
EDWARDS, S. L., SHERFINSKI, J. S. & MARSH, R. E. (1974). *J. Am. Chem. Soc.* **96**, 2593–2597.
FREEMAN, H. C. & GUSS, J. M. (1972). *Acta Cryst.* B**28**, 2090–2096.
FREEMAN, H. C., HUQ, F., ROSALKY, J. M. & TAYLOR, I. F. (1975). *Acta Cryst.* B**31**, 2833–2837.
FREEMAN, H. C. & HUTCHINSON, N. D. (1979). *Acta Cryst.* B**35**, 2045–2050.
GERMAIN, G., MAIN, P. & WOOLFSON, M. M. (1971). *Acta Cryst.* A**27**, 368–376.
International Tables for X-ray Crystallography (1974). Vol. IV, pp. 99–150. Birmingham: Kynoch Press.
MADDEN, J. J., MCGANDY, E. L. & SEEMAN, N. C. (1972). *Acta Cryst.* B**28**, 2377–2382.

Acta Cryst. (1979). B**35**, 2054–2058

The Crystal Structure of Phenylpropanolamine Hydrochloride (2-Amino-1-phenyl-1-propanol Hydrochloride)

BY HANS HEBERT

Department of Medical Biophysics, Karolinska Institutet, S-104 01 *Stockholm, Sweden*

(*Received* 1 *September* 1978; *accepted* 8 *May* 1979)

Abstract

(±)-Phenylpropanolamine or norephedrine hydrochloride, $C_9H_{14}NO^+.Cl^-$, crystallizes in the noncentrosymmetric space group $P2_1$. The unit-cell dimensions are $a = 14{\cdot}519\ (10)$, $b = 9{\cdot}456\ (3)$, $c = 7{\cdot}433\ (9)$ Å, $\beta = 103{\cdot}50\ (2)°$. The structure was determined by the Patterson method and refined by a full-matrix least-squares procedure to an R value of 0·032 for 1756 statistically significant observed reflexions collected by diffractometry. The two optical isomers of the phenylpropanolamine molecule have different conformations in the crystal; one has an extended *trans* conformation while the other is folded into a *gauche* form. The hydrogen-bonded interactions, holding the structure together in the b and c directions, may have an important influence on the molecular conformations.

Introduction

Phenylpropanolamine is an adrenergic drug, widely used as an orally active nasal decongestant. Its vasoconstrictor potency is comparable to that of ephedrine.

0567-7408/79/092054-05$01.00