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Nucleic Acid Binding Drugs. II.* Proflavine Free Base

BY A. ACHARI AND S. NEIDLE

Department of Biophysics, King's College, 26–29 Drury Lane, London WC2B 5RL, England

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Abstract. $C_{13}H_{11}N_3.H_2O$, orthorhombic, $Cmc2_1$, $a=14{\cdot}493$ (8), $b=14{\cdot}675$ (8), $c=5{\cdot}772$ (5) Å, $D_m=1{\cdot}29$ (1), $D_c=1{\cdot}298$ g cm^{-3} for $Z=4$. Equi-inclination Weissenberg intensities, scanned with an automatic densitometer. The structure, solved by direct methods, was refined to R 0·0928 and R_w 0·0910 for 418 reflexions. The ring system is slightly non-planar, and the crystal structure is characterized by a lack of interplanar stacking.

Introduction. Proflavine (Fig. 1) is a member of the acridine family of drugs, which are believed to act biologically by binding to DNA. It has been suggested that the strong binding that has been observed is due to stacking interactions between aminoacridine rings and the base pairs of the DNA (Lerman, 1961). The structures of two salts of proflavine have been reported – proflavine dihydrochloride (Obendorf, Carrell & Glusker, 1974), and proflavine hemisulphate (Jones & Neidle, 1975). The present study is concerned with the free base, in order to ascertain how the lack of protonation affects the ring geometry and interplanar interactions.

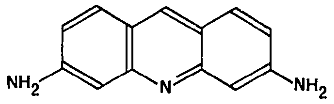

Fig. 1. Proflavine.

Proflavine was crystallized from acetone as deep-red prismatic needles elongated along **c**. Photographs showed that the crystals were orthorhombic, with systematic absences *hkl*; $h+k=2n+1$ and *h*0*l*; $l=2n+1$, thus determining the space group to be $Cmc2_1$ (No. 36), $C2cm$ (alternative setting of No. 40), or $Cmcm$ (No. 63). Since $Z=4$, and the molecules can only have *m* or twofold symmetry, space group *Cmcm* is unreasonable since it would impose *mm* symmetry on a proflavine. The short *c* axis also excludes *C*2*cm* as this has mirror planes (on which the molecules would have to lie) at $c=\frac{1}{4},\frac{3}{4}$. The choice of $Cmc2_1$ was confirmed by the analysis.

Cell dimensions were obtained from calibrated precession (Mo $K\alpha$) photographs. Intensities were collected by the equi-inclination Weissenberg method with multi-film packs. Layers *hk*0–*hk*4 and 0*kl*–1*kl* were photographed with Ni-filtered Cu $K\alpha$ radiation. The films were scanned by the Science Research Council microdensitometer service with an Optronics P-1000 Photoscan. 418 unique, observed reflexions were obtained after interlayer scaling and merging of equivalent reflexions ($R_s=\sum|\bar{I}-I_i|/\sum I_i$, where $\bar{I}$ is the mean of the multiple measurements I_i, $=0{\cdot}087$).

The structure was solved by direct methods with programs written by Dr G. M. Sheldrick which incorporate a multi-solution tangent-formula phasing procedure. The origin was defined with two reflexions such that *h* and *k* are the same parities, from the parity groups *ooe*, *eeo* and *ooo*; they were assigned phases of 0°. The *E* map from the sixth most consistent set revealed the complete ring structure. A subsequent

Table 1. *Final positional* (× 10^4) *and anisotropic thermal* (Å^2 × 10^3) *parameters for the non-hydrogen atoms, with standard deviations in parentheses*

The thermal parameters are of the form $\exp[-2\pi^2(h^2a^{*2}U_{11}+k^2b^{*2}U_{22}+l^2c^{*2}U_{33}+2hka^*b^*U_{12}+2hla^*c^*U_{13}+2klb^*c^*U_{23})]$.

	x	y	z	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
C(1)	0	5867 (7)	8930 (0)	72 (7)	36 (6)	22 (6)	−17 (6)	0	0
N(2)	0	6753 (6)	4638 (27)	41 (4)	39 (6)	39 (7)	7 (4)	0	0
C(3)	−792 (5)	6510 (5)	5643 (29)	41 (4)	33 (4)	42 (7)	−9 (4)	2 (3)	13 (4)
C(4)	−1641 (5)	6708 (6)	4503 (26)	46 (4)	50 (6)	47 (7)	4 (4)	6 (3)	1 (3)
C(5)	−2490 (5)	6488 (7)	5432 (32)	40 (5)	41 (5)	60 (7)	−8 (5)	0 (4)	−6 (3)
C(6)	−2503 (6)	6044 (6)	7684 (31)	53 (6)	47 (5)	47 (6)	18 (5)	18 (4)	−4 (3)
C(7)	−1712 (5)	5824 (5)	8711 (27)	47 (4)	36 (5)	49 (7)	14 (5)	7 (4)	−4 (3)
C(8)	−841 (5)	6067 (5)	7852 (28)	50 (4)	27 (4)	40 (7)	0 (4)	5 (4)	3 (3)
N(9)	−3296 (4)	6593 (5)	4241 (33)	48 (4)	64 (6)	64 (6)	6 (5)	3 (4)	8 (3)
O(10)†	0	8350 (6)	12213 (36)	46 (4)	56 (6)	116 (10)	23 (6)	0	0

† O(10) refers to the water oxygen atom.

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* Part I: Jones & Neidle (1975).

difference synthesis showed the position of an (unexpected) water of crystallization. Full-matrix least-squares refinement with individual isotropic thermal parameters gave an R of 0·132. A difference synthesis revealed the positions of all the H atoms, except one attached to H_2O. The position of this H was calculated from geometric considerations. After full-matrix least-squares refinement with the non-hydrogen atoms assigned individual anisotropic thermal parameters, and all H parameters kept fixed, R was 0·0928 and R_w was 0·0910; at this stage refinement was judged to be complete. A weighting scheme of the form $w=1/\{\sigma^2|F|+0{\cdot}021238F^2\}$ was used. Tables 1 and 2 list the final positional and thermal parameters.*

Table 2. *Fractional coordinates for the hydrogen atoms*

The last two digits of the atom numbering denote the atom to which each hydrogen is bonded. Each hydrogen atom was assigned the thermal parameter of its bonded atom.

	x	y	z
H(101)	0	586	1069
H(204)	−168	690	260
H(306)	−324	576	796
H(407)	−160	537	970
H(509)	−326	696	290
H(609)	−399	676	468
H(710)	0	894	287
H(710)	0	765	1278

The average X–H distance is 1·03 (15) Å.

Table 3. *Bond lengths* (Å) *and angles* (°) *in the asymmetric unit*

Estimated standard deviations are in parentheses. C(3)′ and C(8)′ are related to C(3) and C(8) by the mirror symmetry of the molecule.

C(1)–C(8)	1·400 (10)	C(5)–C(6)	1·454 (12)
N(2)–C(3)	1·335 (10)	C(5)–N(9)	1·364 (12)
C(3)–C(4)	1·425 (12)	C(6)–C(7)	1·330 (12)
C(3)–C(8)	1·433 (11)	C(7)–C(8)	1·401 (10)
C(4)–C(5)	1·380 (12)		
C(8)–C(1)–C(8)′	121·1 (23)	C(4)–C(5)–N(9)	122·8 (10)
C(3)–N(2)–C(3)′	118·7 (10)	C(6)–C(5)–N(9)	119·3 (8)
N(2)–C(3)–C(4)	119·1 (9)	C(5)–C(6)–C(7)	119·7 (8)
C(4)–C(3)–C(8)	117·5 (8)	C(6)–C(7)–C(8)	123·8 (8)
C(3)–C(4)–C(5)	122·8 (10)	C(1)–C(8)–C(3)	116·6 (8)
C(4)–C(5)–C(6)	117·6 (8)	C(3)–C(8)–C(7)	118·4 (8)

Discussion. Fig. 2 shows a projection of the molecule with the numbering scheme; Table 3 details the intramolecular bond lengths and angles. Proflavine has crystallographically-imposed m symmetry, with C(1) and N(2) lying on the mirror plane, and the bond lengths and angles show no significant differences from those in proflavine hemisulphate (Jones & Neidle, 1975), which is protonated at N(2), apart from a not unexpected shortening of N(2)–C(3) and lengthening of C(3)–C(4) in the base compared to the salt. The proflavine ring is significantly non-planar (Table 4), as is the asymmetric unit, N(9) being the most out-of-plane atom. The two mirror-related halves of the molecule are inclined at 5·7° to each other, and the two outer rings [excluding N(9) and its mirror-related N(9)′] are at 3·8° to each other. Similar bucklings have been observed in aminoacridine structures, *e.g.* in proflavine hemisulphate (Jones & Neidle, 1975), and acridines II and III (Phillips, 1956; Phillips, Ahmed &

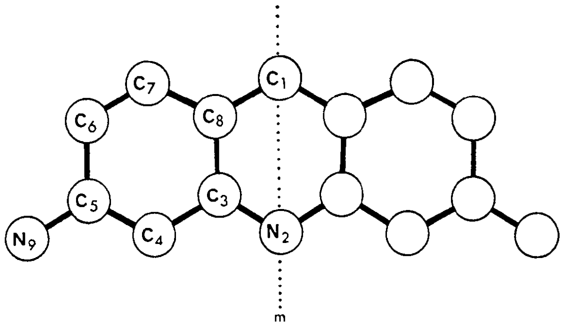

Fig. 2. A projection of the molecule, drawn perpendicular to the ring system. The numbering system used is shown.

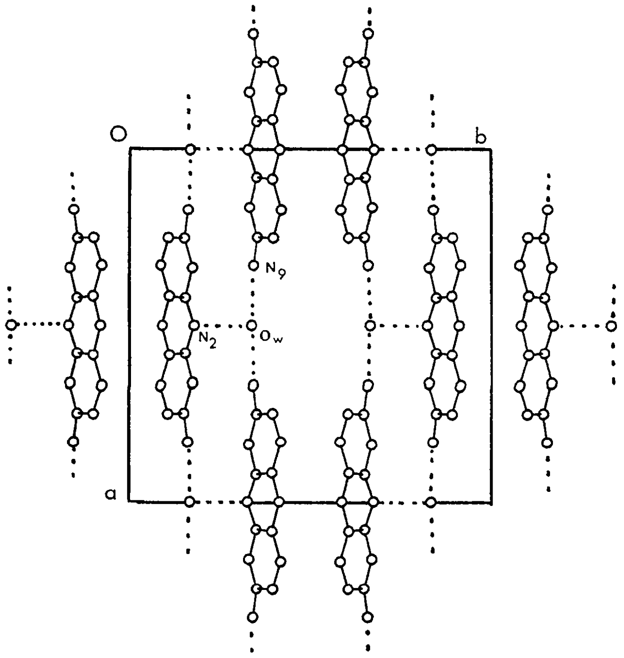

Fig. 3. The c projection of the crystal structure. Dashed lines represent hydrogen bonds.

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* A table of structure factors has been deposited with the British Library Lending Division as Supplementary Publication No. SUP 31782 (4 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

Table 4. *Deviations* (Å) *of atoms from the least-squares planes for various parts of the molecule*

C(3)′ through N(9)′ are generated from the asymmetric unit by the molecular mirror symmetry. Atoms marked with an asterisk have been included in the calculation of the plane.

C(1)	−0·033*	0·004
N(2)	0·000*	0·009
C(3)	0·003*	0·000*
C(4)	0·025*	−0·006*
C(5)	0·042*	−0·003*
C(6)	0·052*	−0·021*
C(7)	−0·023*	−0·028*
C(8)	0·006*	0·016*
N(9)	−0·074*	−0·146
C(3)′	−0·110	
C(4)′	−0·211	
C(5)′	−0·317	
C(6)′	−0·308	
C(7)′	−0·269	
C(8)′	−0·114	
N(9)′	−0·549	

Barnes, 1960), although those observed here seem particularly marked. They are most probably due to intermolecular interactions; it may be significant that proflavine, like the hemisulphate, contrasts with most other aminoacridine crystal structures in not being highly stacked.

The crystal structure (Fig. 3) is shown in **c** projection. The molecules are held together by a network of hydrogen bonds between the proflavine N atoms and H_2O molecules, which are situated on crystallographic mirrors. N(2)–O(10) is 2·703 Å, with the H_2O acting as donor. Each H_2O is also hydrogen bonded (3·008 Å) to two symmetry-related N(9) atoms in adjacent molecules. The proflavine bases are notably unstacked in the lattice, with only minimal overlap between a molecule and its *C*-centred mate.

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Indium Polytelluride In_2Te_5

BY H. H. SUTHERLAND, J. H. C. HOGG AND P. D. WALTON
Physics Department, The University of Hull, Hull, HU6 7RX, England

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Abstract. In_2Te_5, $M=867·64$, monoclinic, Cc; $a=4·39$ (1), $b=16·39$ (1), $c=13·52$ (1) Å, $\beta=91·65$ (5)°, $D_m=5·95$, $D_c=5·94$ g cm^{-3}; $U=969·5$ Å^3, $Z=4$, $F(000)=1432$. The structure was solved from Patterson syntheses with Mo $K\alpha$ X-ray data and refined by block-diagonal least squares to $R=8\%$ for 1223 structure factors. The material is composed of two sheets of atoms running perpendicular to **c***. These are constructed of chains of four-membered In–Te rings; each In is tetrahedrally coordinated indicating that it may be thought of as being sp^3 hybridized with an average In–Te bond of 2·832 (6) Å, alternating with, and cross-linked by, groups of three Te atoms which on an ionic description are $(Te_3)^{2-}$ polyanions. The average Te–Te bond in this anion is 2·837 Å with an included angle of 100·1 (2)°.

Introduction. Cell parameters for a phase, In_2Te_5, have been quoted (Schubert, Dorre & Gunzel, 1954; Gerasimov, Abbasov & Nikolskaya, 1962) and the existence of a phase with this formula was postulated as a result of a DTA and X-ray investigation of the In–Te system (Grochowski, Mason, Schmitt & Smith, 1964). Following the phase diagram produced by Grochowski *et al.*, an intimate mixture of In and Te in the correct stoichiometric proportions to produce In_2Te_5 was placed in a sealed evacuated pyrolysed tube and heated to 550°C. This temperature was maintained for 24 h whilst the tube was shaken to ensure mixing. The sample was then directionally frozen at 2 mm h^{-1} to 400°C and was held there for 48 h before being allowed to cool slowly. This process was repeated with starting compositions to either side of In_2Te_5. In all cases the resulting boules were inhomogeneous but did contain regions of shiny black lamellar material from which crystals were extracted which proved to be In_2Te_5. The density measured experimentally by toluene immersion was 5·95 g cm^{-3}. 1223 reflexions, of which 57 were recorded as zero were collected from Weissenberg photographs taken about **a** with multiple-film packs and Mo $K\alpha$