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9,10-Anthracenedicarbaldehyde Bis[(4,5-dihydro-1*H*-imidazol-2-yl)hydrazone] Acetic Acid Hydrochloric Acid Trihydrate Salt (Bisantrene)

By Robert B. Bates,* Sue A. Roberts and Teruna J. Siahaan

Department of Chemistry, University of Arizona, Tucson, Arizona 85721, USA

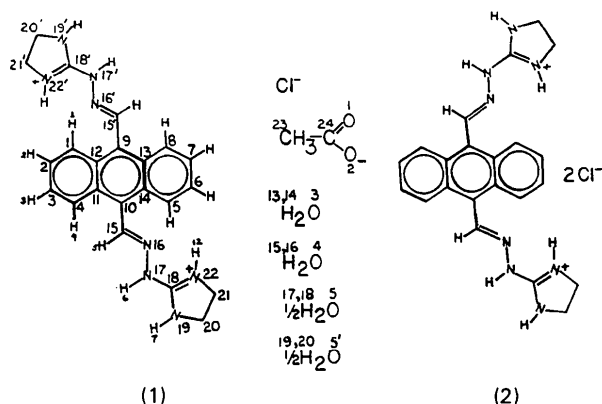and Thiruppuva Gnanasambandan and Samuel H. Yalkowsky

Department of Pharmaceutical Sciences, University of Arizona, Tucson, Arizona 85721, USA

Abstract. $C_{22}H_{24}N_8^{2+} \cdot C_2H_3O_2^- \cdot Cl^- \cdot 3H_2O$, $M_r = 549 \cdot 0$, triclinic, $P\bar{1}$, $a = 8 \cdot 022$ (2), $b = 14 \cdot 175$ (5), $c = 14 \cdot 307$ (5) Å, $\alpha = 109 \cdot 70$ (3), $\beta = 103 \cdot 70$ (2), $\gamma = 106 \cdot 25$ (2)°, $U = 1368 \cdot 1$ Å^3, $Z = 2$, $D_m = 1 \cdot 33$, $D_x = 1 \cdot 33$ g cm^{-3}, Mo $K\alpha$, $\lambda = 0 \cdot 7173$ Å, $\mu = 1 \cdot 84$ cm^{-1}, $F(000) = 580$, $T = 293$ K, final $R = 0 \cdot 060$ for 2245 observed reflections. The unit cell of the antitumor agent bisantrene contains two independent molecules, each with a center of symmetry and *trans*-arranged side chains. In one molecule all non-H atoms are approximately coplanar (one π system for the dication) whereas in the other there is a significant bend (43°) about the first single bond in the side chains, which effectively separates three π systems. All of the rings are involved in stacking of the π systems along the a axis.

Introduction. Although the antitumor agent bisantrene [also called 'orange crush', (1) (Murdock *et al.*, 1982; Feigon, Denny, Leupin & Kearns, 1984] is now used commercially, its mechanism of action is not known. Surprisingly, no X-ray structure has been reported as yet for it, probably because the dihydrochloride (the usual form of the drug) does not form suitably large crystals. It has been proposed that it intercalates into DNA, preferring AT base pairs (Feigon *et al.*, 1984). When excellent orange crystals were found to grow from a solution of bisantrene dihydrochloride buffered with calcium acetate, we decided to carry out an X-ray study on them.

(1)   (2)

Experimental. Orange crystals grown by slow evaporation from pH 5–6 calcium acetate buffer. D_m by flotation. Crystal dimensions $0 \cdot 20 \times 0 \cdot 25 \times 0 \cdot 25$ mm. Syntex $P2_1$ diffractometer. Cell constants from 20 reflections with $3 \le 2\theta \le 24°$. No absorption correction. $2\theta_{max} = 45°$. Range of *hkl*: 0–8, −15–14, −14–10. No decay correction, two check reflections every 98 data points showed only $1 \cdot 3\%$ change during data collection. 2245 of 3544 reflections with $I > 3\sigma(I)$ used in F^2 refinement, $R_{int} = 0 \cdot 014$. Structure solved by *MULTAN*80 (Main *et al.*, 1980) using 361 highest E values; 36 non-H atoms found in first E map, remaining three in difference map. Refinement of non-H atoms with isotropic temperature factors gave $R = 0 \cdot 10$; final refinement (342 parameters) of non-H atoms with anisotropic temperature factors [except O(5) and O(5′),

the disordered water oxygen atoms, which were given isotropic temperature factors] after adding H atoms in observed or calculated positions with isotropic temperature factors of $5 \cdot 0 \, \text{Å}^2$; $R = 0 \cdot 060$, $wR = 0 \cdot 074$, $S = 2 \cdot 6$, weighting scheme of Corfield, Doedens & Ibers (1967), with $p = 0 \cdot 03$. $(\Delta/\sigma)_{max} = 0 \cdot 15$. $\Delta\rho = -0 \cdot 4 - 0 \cdot 5 \, \text{e} \, \text{Å}^{-3}$. No anomalous-dispersion corrections. Atomic scattering factors from Cromer & Waber (1974). Programs *SDP* (Frenz, 1978), including plotter program *ORTEP* (Johnson, 1976), run on PDP 11/34a.

Discussion. Fig. 1 shows the two independent molecules [(1) and (1a)] in the unit cell, Table 1 lists the final positional and isotropic thermal parameters, Table 2 gives bond distances and bond angles.* Both molecules possess centers of symmetry, and thus a *trans* arrangement of side chains rather than the *cis* arrangement (2) usually drawn. In molecule (1a) the whole π system is approximately planar, whereas in molecule (1) there is a substantial twist ($43°$) about the C(10)—C(15) bond, which gives three separate π systems.

Bond distances and angles agree well between the two molecules (Table 2). The carbon—carbon bonds of the anthracene ring range from $1 \cdot 35$ to $1 \cdot 44 \, \text{Å}$. The C(15)—N(16) and C(15a)—N(16a) bonds are very short, $1 \cdot 273$ (7) and $1 \cdot 260$ (4) Å, indicating considerable double-bond character, as in the resonance form usually drawn (1). The C(18)—N(22) and C(18a)—N(22a) bonds are shorter than the other C—N bonds to these carbons, indicating the former bonds to have more double-bond character than do the latter. The twist about the C(10)—C(15) bond results in a slight lengthening of this bond relative to C(10a)—C(15a), and a relative lengthening of C(15)—N(16) relative to C(15a)—N(16a).

The side chains are largely planar; the twists about C(15)—N(16), N(16)—N(17), and N(17)—C(18) bonds are within $7 \cdot 5$ (3)° of 0 or 180° in both molecules. The torsion angle C(11a)—C(10a)—C(15a)—N(16a) is $4 \cdot 5$ (3)°, indicating near planarity of all atoms of the π system in molecule (1a). However, in molecule (1), C(11)—C(10)—C(15)—N(16) is $42 \cdot 7$ (3)°, effectively isolating three π systems from one another. The five-membered ring in molecule (1a) is almost perfectly flat [torsion angles around the ring within $1 \cdot 0$ (3)° of 0°], whereas that in molecule (1) is much more puckered [corresponding angles $-4 \cdot 1$ (3), $8 \cdot 8$ (3) up to $9 \cdot 6$ (3)° from 0°]. The anthracene systems are nearly planar [greatest deviation of a ring atom from the plane

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* Lists of structure factors, anisotropic thermal parameters and H-atom coordinates have been deposited with the British Library Lending Division as Supplementary Publication No. 42481 (24 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.
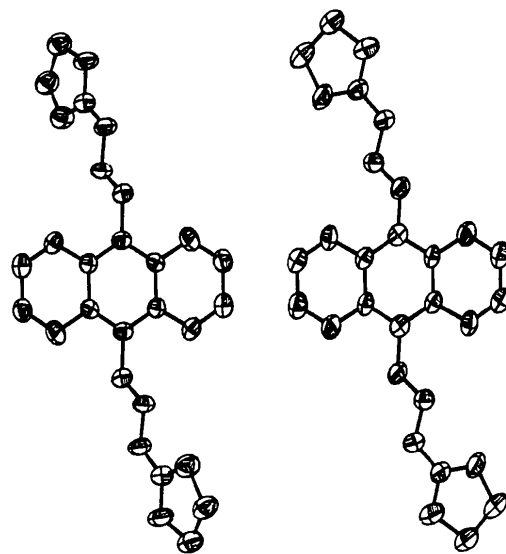

Fig. 1. *ORTEP* drawings of molecule (1) (left) and molecule (1a) (right) $\perp$ to the anthracene rings, with 50% probability thermal ellipsoids.

Table 1. *Positional parameters and their e.s.d.'s*

	x	y	z	$B_{eq}(\text{Å}^2)$
C1	0·8074 (2)	0·1913 (1)	0·7207 (1)	6·11 (4)
O(1)	0·2516 (6)	0·3845 (3)	0·6214 (3)	7·6 (1)
O(2)	0·2314 (6)	0·3720 (3)	0·4622 (3)	6·3 (1)
O(3)	0·1120 (7)	0·4581 (3)	0·3233 (3)	8·2 (1)
O(4)	0·1748 (7)	0·6830 (3)	0·4310 (3)	9·3 (2)
O(5)	0·221 (1)	0·4952 (6)	0·8120 (6)	7·3 (2)*
O(5')	0·199 (1)	0·3687 (6)	0·7951 (7)	7·8 (2)*
N(16)	0·1458 (5)	0·0870 (3)	0·2962 (3)	3·8 (1)
N(16a)	0·1359 (5)	0·7460 (3)	0·9801 (3)	4·2 (1)
N(17)	0·1943 (6)	0·1599 (3)	0·4006 (3)	4·5 (1)
N(17a)	0·0388 (5)	0·6921 (3)	1·0279 (3)	4·2 (1)
N(19)	0·2761 (6)	0·1865 (3)	0·5775 (3)	5·3 (1)
N(19a)	−0·2024 (6)	0·5407 (3)	1·0067 (3)	5·3 (1)
N(22)	0·2229 (6)	0·0267 (3)	0·4573 (3)	5·3 (1)
N(22a)	−0·1565 (6)	0·5447 (3)	0·8635 (3)	4·7 (1)
C(1)	−0·2843 (6)	−0·2134 (3)	−0·1059 (3)	3·7 (1)
C(1a)	0·4921 (7)	0·9548 (3)	0·7893 (3)	4·2 (1)
C(2)	−0·3642 (7)	−0·2593 (3)	−0·0499 (4)	4·4 (1)
C(2a)	0·3691 (7)	0·8593 (4)	0·7057 (3)	4·4 (1)
C(3)	−0·3063 (7)	−0·2030 (3)	0·0608 (3)	4·5 (1)
C(3a)	0·2447 (7)	0·7822 (3)	0·7217 (4)	4·3 (1)
C(4)	−0·1709 (6)	−0·1018 (3)	0·1132 (3)	4·0 (1)
C(4a)	0·2457 (6)	0·8001 (3)	0·8209 (3)	4·0 (1)
C(10)	0·0581 (6)	0·0584 (3)	0·1124 (3)	2·9 (1)
C(10a)	0·3740 (6)	0·9191 (3)	1·0168 (3)	3·2 (1)
C(11)	−0·0797 (6)	−0·0490 (3)	0·0596 (3)	3·1 (1)
C(11a)	0·3724 (6)	0·8994 (3)	0·9132 (3)	3·2 (1)
C(12)	−0·1383 (6)	−0·1069 (3)	−0·0543 (3)	3·0 (1)
C(12a)	0·4986 (6)	0·9804 (3)	0·8960 (3)	3·2 (1)
C(15)	0·1169 (6)	0·1245 (3)	0·2273 (3)	3·4 (1)
C(15a)	0·2517 (6)	0·8420 (3)	1·0419 (3)	3·9 (1)
C(18)	0·2293 (6)	0·1248 (3)	0·4749 (3)	4·0 (1)
C(18a)	−0·1005 (6)	0·5962 (3)	0·9669 (3)	3·8 (1)
C(20)	0·2933 (8)	0·1245 (4)	0·6392 (4)	5·7 (2)
C(20a)	−0·3460 (7)	0·4390 (4)	0·9218 (4)	5·4 (2)
C(21)	0·2790 (8)	0·0180 (4)	0·5583 (4)	5·5 (2)
C(21a)	−0·3156 (8)	0·4424 (4)	0·8235 (4)	6·1 (2)
C(23)	0·351 (1)	0·5492 (4)	0·6031 (5)	8·4 (2)
C(24)	0·2723 (7)	0·4263 (4)	0·5589 (4)	5·0 (1)

* Starred atoms were refined isotropically. Anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as $B_{eq} = 8\pi^2(U_{11} + U_{22} + U_{33})/3$.

0·016 (5) Å]; the side-chain atoms are within 1·334 (6) Å of the plane in molecule (1a) but up to 2·647 (7) Å away from the plane [C(21)] in the case of twisted molecule (1). The angle between the anthracene planes is 6·5 (4)°.

The packing diagram (Fig. 2) shows a chloride atom associated with molecule (1a) as expected, but the X-ray study shows the other molecule (1) to be associated instead with an acetate ion (from buffer) via H bonds from N(17) to O(2) and N(19) to O(1). In addition, there are two undisordered water molecules, containing O(3) and O(4), and one water molecule disordered between two positions, containing O(5) and O(5'), each with occupancy factor 0·5; since O(5) and O(5') are only 1·68 (1) Å apart, they cannot be present in the same cell.

The complete hydrogen-bonding scheme is shown in Fig. 2. The hydrogens in water molecules involving O(4), O(5) and O(5') were calculated to be directly on the line to the acceptor atoms. The disorder occurs because it is equal energetically to have O(5) H-bonding to O(3) and O(5') H-bonding to Cl⁻.

The anthracene rings of molecule (1) form stacks with anthracene rings of molecule (1a) along the a axis. The five-membered rings of both molecules also stack in the a direction, but with molecules of the same type in adjacent cells in the c direction.

The twist of the side chains in molecule (1) probably occurs largely to permit a good arrangement of H-bonds, e.g. it allows N(22) to H-bond to the Cl⁻, which is roughly in the plane of molecule (1a). That these H-bonding forces are sufficient to cause the split into three π systems in molecule (1) indicates that not much resonance energy is gained by allowing delocalization over the whole π system in the trans slightly twisted coplanar form (1); it remains to be demonstrated what conformation of the molecule intercalates into DNA.

Table 2. Bond lengths (Å) and bond angles (°)

Numbers in parentheses are e.s.d.'s in the least significant digits.

O(1)	C(24)	1·246 (8)	C(1a)	C(2a)	1·356 (5)
O(2)	C(24)	1·241 (6)	C(1a)	C(12a)	1·430 (7)
O(5)	O(5')	1·676 (13)	C(2)	C(3)	1·398 (6)
N(16)	N(17)	1·382 (4)	C(2a)	C(3a)	1·382 (7)
N(16)	C(15)	1·273 (7)	C(3)	C(4)	1·348 (5)
N(16a)	N(17a)	1·390 (6)	C(3a)	C(4a)	1·353 (7)
N(16a)	C(15a)	1·260 (4)	C(4)	C(11)	1·425 (7)
N(17)	C(18)	1·323 (7)	C(4a)	C(11a)	1·438 (4)
N(17a)	C(18a)	1·321 (4)	C(10)	C(11)	1·413 (4)
N(19)	C(18)	1·322 (5)	C(10)	C(14)	1·404 (7)
N(19)	C(20)	1·451 (8)	C(10)	C(15)	1·467 (5)
N(19a)	C(18a)	1·332 (7)	C(10a)	C(11a)	1·409 (7)
N(19a)	C(20a)	1·452 (5)	C(10a)	C(14a)	1·419 (4)
N(22)	C(18)	1·310 (7)	C(10a)	C(15a)	1·455 (7)
N(22)	C(21)	1·465 (7)	C(11)	C(12)	1·439 (5)
N(22a)	C(18a)	1·302 (6)	C(11a)	C(12a)	1·436 (6)
N(22a)	C(21a)	1·455 (6)	C(20)	C(21)	1·514 (7)
C(1)	C(2)	1·355 (8)	C(20a)	C(21a)	1·497 (10)
C(1)	C(12)	1·430 (5)	C(23)	C(24)	1·512 (7)

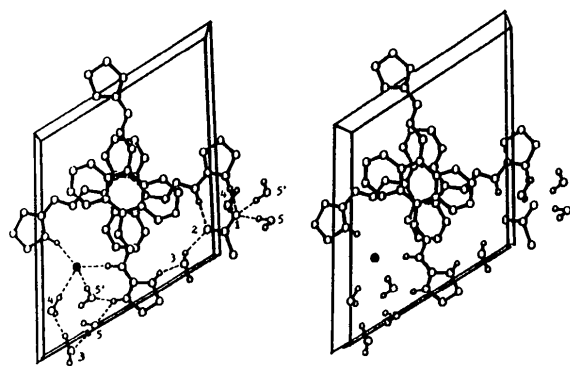|							
N(17)	N(16)	C(15)	115·4 (4)	C(4a)	C(11a)	C(10a)	122·5 (4)
N(17a)	N(16a)	C(15a)	114·8 (4)	C(4a)	C(11a)	C(12a)	117·2 (4)
N(16)	N(17)	C(18)	117·3 (4)	C(10a)	C(11a)	C(12a)	120·3 (3)
N(16a)	N(17a)	C(18a)	118·8 (4)	C(1)	C(12)	C(10)	121·6 (4)
C(18)	N(19)	C(20)	110·9 (4)	C(1)	C(12)	C(11)	117·7 (4)
C(18a)	N(19a)	C(20a)	110·5 (4)	C(10)	C(12)	C(11)	120·7 (3)
C(18)	N(22)	C(21)	110·4 (4)	N(16)	C(15)	C(10)	123·2 (4)
C(18a)	N(22a)	C(21a)	110·5 (5)	N(16a)	C(15a)	C(10a)	128·2 (4)
C(2)	C(1)	C(12)	121·5 (4)	N(17)	C(18)	N(19)	123·0 (5)
C(2a)	C(1a)	C(12a)	122·2 (5)	N(17)	C(18)	N(22)	125·1 (4)
C(1)	C(2)	C(3)	120·6 (4)	N(19)	C(18)	N(22)	111·9 (5)
C(1a)	C(2a)	C(3a)	120·3 (5)	N(17a)	C(18a)	N(19a)	122·2 (4)
C(2)	C(3)	C(4)	120·3 (5)	N(17a)	C(18a)	N(22a)	111·8 (3)
C(2a)	C(3a)	C(4a)	120·6 (3)	N(19a)	C(18a)	N(22a)	111·8 (3)
C(3)	C(4)	C(11)	122·1 (4)	N(19)	C(20)	C(21)	102·8 (4)
C(3a)	C(4a)	C(11a)	122·1 (4)	N(19a)	C(20a)	C(21a)	103·1 (4)
C(14)	C(10)	C(15)	117·6 (3)	N(22)	C(21)	C(20)	103·1 (5)
C(11a)	C(10a)	C(14a)	119·4 (4)	N(22a)	C(21a)	C(20a)	104·1 (4)
C(11a)	C(10a)	C(15a)	124·1 (3)	O(1)	C(24)	O(2)	123·2 (5)
C(4)	C(11)	C(10)	123·1 (4)	O(1)	C(24)	C(23)	118·3 (5)
C(4)	C(11)	C(12)	117·7 (3)	O(2)	C(24)	C(23)	118·5 (6)

Fig. 2. ORTEP stereoviews of a unit cell, ⊥ a, b vertical. The origin is displaced to 0·5, 0·5, 0·5 to put the center of a molecule at the center of the cell depicted. Each of the hydrogen bonds is shown once as a dashed line. Numbers indicate oxygen atoms, and the darkened atom is chlorine.

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