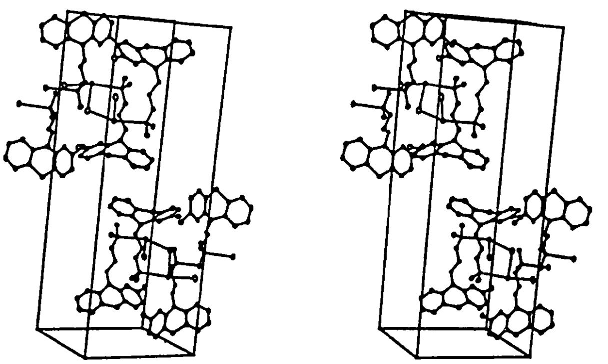

Fig. 2. Stereoscopic packing diagram of the contents of the unit cell showing the H-bond network.

There is an H-bond network involving the protonated N atoms [N(2) and N(2)′], the water molecule and the chloride ions (Cl and Cl′). There are H bonds between the chloride ions and the amine H atoms [Cl···HN(2)′, 2·021 (2) and Cl′···HN(2), 2·089 (5) Å; Cl···HN(2)′–N(2)′, 173·2 (4) and Cl′···HN(2)–N(2), 165·3 (4)°]. Additionally, Cl′ is H-bonded to the water molecule through HO(2) [Cl′···HO(2), 2·248 (6) Å and Cl′···HO(2)–O(1), 104·8 (3)°]. Fig. 2 shows the H-bonding scheme between the molecules and ions in the unit cell.

We would like to thank the University of New Orleans and Dr Edwin D. Stevens for allowing us to collect data on their instrument and for the helpful advice. The National Institutes of Health (MBRS-RR-08008) and the donors of the Petroleum Research Fund administered by the American Chemical Society are also gratefully thanked.

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*Acta Cryst.* (1986). C**42**, 1085–1087

# Crystallographic Characterization of the Anticancer Drug Bisantrene* Cocrystallized with Pyridinium Chloride

By Cortlandt G. Pierpont

*Department of Chemistry, University of Colorado, Boulder, Colorado* 80309, *USA*

and Stanley A. Lang Jr

*Lederle Laboratories, American Cyanamid Company, Pearl River, New York* 10965, *USA*

(*Received* 16 *October* 1985; *accepted* 26 *February* 1986)

**Abstract.** $C_{22}H_{24}N_8^{2+}.C_5H_6N^+.3Cl^-.2H_2O$, $M_r = 623{\cdot}0$, monoclinic, $C2/c$, $a = 23{\cdot}410\,(4)$, $b = 9{\cdot}694\,(2)$, $c = 13{\cdot}745\,(3)$ Å, $\beta = 104{\cdot}76\,(2)°$, $V = 3016{\cdot}3\,(4)$ Å$^3$, $Z = 4$, $D_m = 1{\cdot}39$, $D_x = 1{\cdot}372$ g cm$^{-3}$, Mo $K\alpha$, $\lambda = 0{\cdot}71069$ Å, $\mu = 3{\cdot}44$ cm$^{-1}$, $F(000) = 1304$, $T = 293$ K, $R = 0{\cdot}045$ for 1241 unique reflections [$I \geq 3{\cdot}0\sigma(I)$]. The crystal structure consists of stacks of alternating bisantrenium and pyridinium cations. Adjacent stacks are linked by strong interstack

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* 9,10-Anthracenedicarboxaldehyde bis[(4,5-dihydro-1*H*-imidazol-2-yl)hydrazone].

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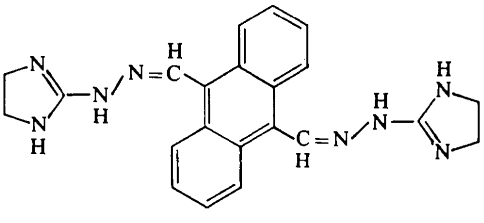
H bonds to $Cl^-$ anions. Strong interactions with $Cl^-$ anions may result in precipitation of the anticancer drug during physiological tests.

**Introduction.** Bisantrene (I) (Citarella, Wallace, Murdock, Angier & Durr, 1980) is a second generation anticancer drug currently in final stages of Phase II trials (Spiegel *et al.*, 1982; Von Hoff *et al.*, 1981).



(I)

Its major toxic effects in human patients are reversible leukopenia and local cutaneous reactions. Intravascular injection of the drug is often accompanied by crystallization or precipitation of the drug near the site of deposition. A recent study has shown that locally high concentrations of bisantrene do not independently contribute to local complications (Tseng & Safa, 1983; Powis & Korvach, 1983). The drug appears to act as an intercalating agent (Lown, Hanstock, Bradley & Scraba, 1984; Feigon, Denny, Leupin & Kearns, 1984) but lacks the cardiotoxic effects associated with anthracycline drugs like doxorubicin (Yap, Yap, Blumenschein, Barnes, Schell & Bodey, 1983). In this report we describe the crystal structure of the dihydrochloride salt of bisantrene, the soluble form of the molecule which is administered clinically, isolated from an aqueous ethanol solution also containing pyridinium chloride. Cocrystallized with the bisantrenium chloride are two water molecules and one formula unit of pyridinium chloride. Interionic interactions in the crystal structure provide insights as to the nature of interactions with planar nucleic acid bases and to the forces which might be responsible for precipitation in human tests.

**Experimental.** Suitable crystals grown at room temperature from ethanol solution. Orange–red parallelepiped crystal: 0·41 × 0·37 × 0·22 mm. Syntex $P\bar{1}$ diffractometer, graphite monochromator. Lattice parameters from least-squares refinement of 20 reflections ($20 \leq 2\theta \leq 30°$). No absorption correction. Max. $(\sin\theta)/\lambda = 0{\cdot}54$ Å$^{-1}$ ($-25 \leq h \leq 25$; $0 \leq k \leq 10$; $0 \leq l \leq 14$). No significant intensity variations of standard reflections. 1990 unique measured reflections: 1241 observed [$I \geq 3{\cdot}0\sigma(I)$]. Direct methods: *MULTAN*80 (Main *et al.*, 1980). Refinement (on $F$): *SHELX*76 (Sheldrick, 1976). Full-matrix least-squares anisotropic refinement on all nonhydrogen atoms. $w = 1/\sigma^2(F)$. Final $R = 0{\cdot}045$, $wR = 0{\cdot}051$ for 1241 observed reflections, 193 parameters and an observation to parameter ratio of 6·4. Max., min. peaks in final $\Delta F$ synthesis: 0·31, −0·22 e Å$^{-3}$. Max. $\Delta/\sigma = 0{\cdot}16$ [$y$ of C(14)]. Scattering factors from *SHELX*76 (Sheldrick, 1976). H-atom positions determined from difference map and included with fixed contributions in subsequent cycles of refinement. Atoms located on the twofold axis of the unit cell were refined with occupancy factors of 0·5.

**Discussion.** Final atomic coordinates are given in Table 1 and bond lengths and angles in Table 2.* The bisantrenium ion is located about a crystallographic inversion center with the side chains extended in an $\omega$ conformation. A view of the cation is shown in Fig. 1. Rotation about the C(4)–C(8) bond breaks up the planarity of the molecule relieving potential steric interactions that would exist between N(4) and the ring H bonded to C(6) in an otherwise regularly planar structure. Bond distances within the anthracene ring are normal but lengths within the side chains indicate extended delocalization over bonds from N(1) and N(2) to C(4). Perhaps the most interesting features of the structure are the interactions between molecules and ions in the unit cell. Water molecules are strongly H-bonded to the H atoms bonded to the N(3) atoms. Pyridinium rings are located above and below the anthracene plane along a twofold axis forming a columnar crystal structure with alternating pyridinium and bisantrenium ions. These stacks are further stabilized by relatively strong interactions between chloride ion Cl(1) and H atoms bonded to N(5) of the pyridinium ion (1·95 Å), N(2) of one dihydroimidazolyl side chain (2·22 Å), and the N(2) atom of an adjacent stack, related by the location of this chloride along a crystallographic twofold axis. The remaining chloride ion, Cl(2), is H bonded to the N(2) hydrogen with a Cl···H separation of 2·25 Å and to the water molecule with a length of 2·30 Å. The result is a stable crystal structure due to the effect of stacking interactions and the crosslinks between stacks.

The tendency for the N—H bonds of the bisantrenium ion to form strong H bonds even with chloride ions may be responsible for crystallization of the drug upon injection into the plasma where chloride-ion concentration is relatively high. Bisantrene is known to intercalate with DNA and the structure of the pyridinium stack suggests that the central ring of the anthracene is the preferred site for charge-transfer bonding by a heterocyclic base.

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* Lists of structure factors, anisotropic thermal parameters and H-atom positions have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42873 (9 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

Table 1. *Final atomic coordinates and $U_{eq}$ values*

$U_{eq} = \frac{1}{3}(U_{11} + U_{22} + U_{33})$.

| | $x$ | $y$ | $z$ | $U_{eq}$(Å$^2$) |
|---|---|---|---|---|
| C(11) | 0 | 0·0227 (2) | 0·25 | 0·077 (1) |
| C(12) | 0·29282 (6) | 0·0533 (1) | 0·1991 (1) | 0·081 (1) |
| N(1) | −0·1337 (2) | 0·0277 (4) | 0·1335 (3) | 0·057 (2) |
| N(2) | −0·2201 (1) | −0·0111 (4) | 0·0295 (3) | 0·053 (2) |
| N(3) | −0·1612 (2) | 0·1572 (4) | −0·0143 (3) | 0·054 (2) |
| N(4) | −0·1094 (1) | 0·2301 (4) | 0·0157 (3) | 0·052 (2) |
| C(1) | −0·1710 (2) | 0·0623 (5) | 0·0481 (3) | 0·049 (3) |
| C(2) | −0·1581 (2) | −0·0845 (6) | 0·1794 (4) | 0·071 (3) |
| C(3) | −0·2173 (2) | −0·1111 (5) | 0·1080 (4) | 0·065 (3) |
| C(4) | −0·1024 (2) | 0·3249 (5) | −0·0442 (4) | 0·052 (3) |
| C(5) | −0·0740 (2) | 0·8393 (6) | −0·0500 (4) | 0·075 (4) |
| C(6) | −0·0184 (2) | 0·7885 (5) | −0·0192 (4) | 0·064 (3) |
| C(7) | −0·0077 (2) | 0·6449 (4) | −0·0100 (3) | 0·050 (3) |
| C(8) | −0·0493 (2) | 0·4118 (4) | −0·0201 (3) | 0·046 (3) |
| C(9) | −0·0576 (2) | 0·5545 (4) | −0·0309 (3) | 0·045 (3) |
| C(10) | −0·1147 (2) | 0·6138 (5) | −0·0624 (4) | 0·062 (3) |
| C(11) | −0·1224 (2) | 0·7516 (5) | −0·0729 (4) | 0·071 (3) |
| O(1) | 0·2434 (2) | 0·2481 (4) | 0·3381 (3) | 0·084 (3) |
| N(5) | 0 | 0·3341 (7) | 0·25 | 0·081 (5) |
| C(12) | 0·0522 (3) | 0·3998 (8) | 0·2735 (4) | 0·089 (5) |
| C(13) | 0·0528 (3) | 0·5425 (8) | 0·2745 (4) | 0·099 (6) |
| C(14) | 0 | 0·613 (1) | 0·25 | 0·098 (7) |

Table 2. *Bond lengths* (Å) *and angles* (°) *for bisantrenium pyridinium chloride*

| | | | |
|---|---|---|---|
| N(1)–C(1) | 1·316 (5) | N(1)–C(2) | 1·445 (6) |
| N(2)–C(1) | 1·320 (5) | N(2)–C(3) | 1·440 (6) |
| N(3)–N(4) | 1·373 (5) | N(3)–C(1) | 1·317 (5) |
| N(4)–C(4) | 1·272 (5) | C(2)–C(3) | 1·503 (6) |
| C(4)–C(8) | 1·467 (6) | C(5)–C(6) | 1·356 (7) |
| C(5)–C(11) | 1·386 (7) | C(6)–C(7) | 1·415 (6) |
| C(7)–C(9) | 1·428 (6) | C(8)–C(9) | 1·400 (6) |
| C(9)–C(10) | 1·418 (6) | C(10)–C(11) | 1·351 (7) |
| N(5)–C(12) | 1·342 (7) | C(12)–C(13) | 1·384 (9) |
| C(13)–C(14) | 1·380 (8) | C(7)–C(8) | 1·405 (6) |
| | | | |
| C(2)–N(1)–C(1) | 109·6 (4) | C(3)–N(2)–C(1) | 110·3 (3) |
| C(1)–N(3)–N(4) | 116·8 (4) | C(4)–N(4)–N(3) | 115·3 (4) |
| N(2)–C(1)–N(1) | 112·4 (4) | N(3)–C(1)–N(1) | 125·0 (4) |
| N(3)–C(1)–N(2) | 122·6 (4) | C(3)–C(2)–N(1) | 104·2 (4) |
| C(2)–C(3)–N(2) | 103·5 (4) | C(8)–C(4)–N(4) | 120·6 (4) |
| C(11)–C(5)–C(6) | 120·8 (5) | C(7)–C(6)–C(5) | 121·2 (4) |
| C(9)–C(7)–C(6) | 118·0 (4) | C(9)–C(8)–C(4) | 117·2 (4) |
| C(8)–C(9)–C(7) | 120·1 (4) | C(10)–C(9)–C(7) | 118·1 (4) |
| C(10)–C(9)–C(8) | 121·8 (4) | C(11)–C(10)–C(9) | 121·5 (5) |
| C(10)–C(11)–C(5) | 120·2 (5) | C(13)–C(12)–N(5) | 118·9 (7) |
| C(12)–N(5)–C(12) | 123·4 (8) | C(14)–C(13)–C(12) | 119·2 (7) |
| C(13)–C(14)–C(13) | 120·3 (9) | C(7′)–C(8)–C(9) | 120·9 (4) |
| | | C(9)–C(7)–C(8′) | 119·1 (4) |

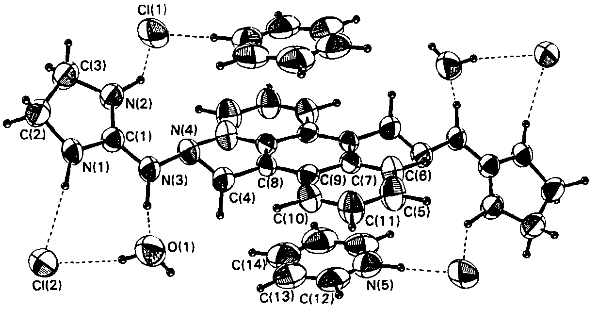

Fig. 1. View showing the stacking interaction between pyridinium and bisantrenium ions and the H bonding to chloride ions. Cl(1) and the pyridinium ring are located along a crystallographic twofold axis. An inversion center is located at the center of the anthracene ring.

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*Acta Cryst.* (1986). C**42**, 1087–1089

# Structure of 2,5-Diamino-3*H*-1,3,4-thiadiazolinium Chloride Monohydrate

By Hitoshi Senda, Hajime Matsuoka and Juro Maruha

*College of Liberal Arts, Kanazawa University, Marunouchi, Kanazawa 920, Japan*

(*Received* 21 *November* 1985; *accepted* 21 *February* 1986)

**Abstract.** $C_2H_5N_4S^+.Cl^-.H_2O$, $M_r = 170·6$, monoclinic, $P2_1/a$, $a = 14·217\ (3)$, $b = 9·526\ (2)$, $c = 5·0497\ (9)$ Å, $\beta = 98·31\ (2)°$, $V = 676·7\ (2)$ Å$^3$, $Z = 4$, $D_m = 1·67$ (by flotation), $D_x = 1·675$ Mg m$^{-3}$, Mo $K\alpha$, $\lambda = 0·71069$ Å, $\mu = 0·127$ mm$^{-1}$, $F(000) = 352$, $T = 293$ K, final $R = 0·027$ for 1083 observed unique

0108-2701/86/081087-03$01.50