

Fig. 2. *PLUTO* (Motherwell & Clegg, 1978) stereodrawing of the molecular packing. H bonding is represented by dotted lines.

The hydroxyphenyl ring is bonded equatorially to the pyrone ring. Although a pseudoaxial conformation has been suggested to be an active form for phyllo dulcin (DuBois, Crosby, Stephenson & Wingard, 1977), this conformation has not been observed in the crystal structures of benzopyrone or dihydroisocoumarin derivatives. The *A* and *C* rings are nearly perpendicular to each other with a dihedral angle of 85.7° . Other flavanones also assume a similar conformation (see Table 3). However, the relative orientation of the phenyl and benzopyrone rings seems to be determined by crystal packing forces since, in solution, *C*(2') and *C*(3') are chemically and magnetically equivalent to *C*(6') and *C*(5') as determined by ^{13}C NMR studies of flavanones (Cotterill, Scheinmann & Stenhouse, 1977).

Two unique $\text{O}-\text{H}\cdots\text{O}$ hydrogen bonds make a two-dimensional hydrogen-bonded molecular layer through the formation of hydrogen-bonded dimers and hexamers (Fig. 2): $\text{O}(7)\cdots\text{O}(4')(1-x, 1-y, 1-z) = 2.805(4)$, $\text{O}(7)-\text{H}(7) = 0.83(5)$, $\text{H}(7)\cdots\text{O}(4') =$

$2.04(5)\text{ \AA}$, $\angle\text{O}(7)-\text{H}\cdots\text{O}(4') = 154(4)^\circ$; $\text{O}(4')\cdots\text{O}(4)(1+x, 0.5-y, 0.5+z) = 2.711(4)$, $\text{O}(4')-\text{H}(4') = 0.77(4)$, $\text{H}(4')\cdots\text{O}(4) = 1.95(5)\text{ \AA}$, $\angle\text{O}(4')-\text{H}\cdots\text{O}(4) = 172(5)^\circ$. There are only van der Waals interactions between these layers.

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The Structure of a Reduction Product of the Cytotoxic Drug Nitracrine

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Abstract. 2,3-Dihydro-2,2-dimethyl-1-[3-(dimethylamino)propyl]-1*H*-pyrimidino[4,5,6-*de*]acridine dihydrochloride, $\text{C}_{21}\text{H}_{28}\text{N}_4^+\cdot 2\text{Cl}^-$, $M_r = 407.11$, monoclinic, $P2_1/c$, $a = 15.351(1)$, $b = 12.108(1)$, $c = 11.559(2)\text{ \AA}$, $\beta = 102.03(1)^\circ$, $V = 2101.4(7)\text{ \AA}^3$, $Z = 4$, $D_m = 1.28(1)$, $D_x = 1.286\text{ g cm}^{-3}$, $\text{Mo K}\alpha$, λ

$= 0.71073\text{ \AA}$, $\mu = 2.68\text{ cm}^{-1}$, $F(000) = 860$, $T = 293\text{ K}$, $R = 0.040$ for 1869 ($I > 2.5\sigma$) reflections. X-ray analysis shows that the nitracrine reduction product, 1-amino-9-(dimethylaminopropyl)acridine, has condensed with one mole of acetone across the primary and secondary amine functions, to form a pyrimidinoacridine ring system. The acridine nucleus suffers a concomitant buckling from planarity.

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Introduction. The clinically used drug nitracrine [1-nitro-9-(dimethylaminopropyl)acridine] (Gniazdowski, Filipski & Choruzy, 1979) has recently been shown to exhibit selective toxicity for mammalian cells under hypoxic conditions (Wilson, Denny, Twigden, Baguley & Probert, 1984). Since this cytotoxicity is the result of selective reduction of the drug under hypoxic conditions to reactive metabolites, the chemistry of such reduction products is of particular interest. It has been found that the ultimate reduction product, 1-amino-9-(dimethylaminopropyl)acridine, reacts rapidly with carbonyl compounds to give stable adducts. The structure of the addition product with acetone has been determined by X-ray crystallography and is shown to be 2,3-dihydro-2,2-dimethyl-1-[3-(dimethylamino)propyl]-1*H*-pyrimidino[4,5,6-*de*]acridine.

Experimental. Crystals were prepared as deep-red prisms. Density measured by flotation in CHCl_3 /hexane. Fragment $0.11 \times 0.22 \times 0.28$ mm mounted on Nonius CAD-4 diffractometer; graphite-monochromated Mo *K* α radiation; unit-cell dimensions from 25 reflections, $24 < 2\theta < 32^\circ$; systematic absences $h0l$, $l \neq 2n$ and $0k0$, $k \neq 2n$ defined space group as $P2_1/c$; 2813 unique reflections, $4 \leq 2\theta \leq 50^\circ$, $[(\sin\theta)/\lambda]_{\text{max}} = 0.5946 \text{ \AA}^{-1}$; 1869 with $I \geq 2.5\sigma(I)$, $0 \leq h \leq 19$, $0 \leq k \leq 15$, $-15 \leq l \leq 15$; three intensity standards checked every 100 reflections showed no non-statistical variation during X-ray exposure; absorption corrections not required because of low μ ; $R_{\text{int}} = 0.016$.

Table 1. Positional parameters ($\times 10^4$)

Temperature factors of anisotropically refined atoms are given in the form of the isotropic equivalent thermal parameter defined as $\frac{1}{3}[a^2\beta_{11} + b^2\beta_{22} + c^2\beta_{33} + ab(\cos\gamma)\beta_{12} + ac(\cos\beta)\beta_{13} + bc(\cos\alpha)\beta_{23}]$.

	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i> (\AA^2)
Cl(1)	3132 (1)	2029 (1)	8610 (1)	3.9
Cl(2)	9701 (1)	1033 (1)	2112 (1)	4.3
N(1)	7651 (2)	785 (2)	4736 (3)	2.3
N(3)	8079 (2)	2259 (3)	6102 (3)	3.2
N(4')	8383 (2)	-3222 (2)	5043 (3)	3.1
N(8)	5074 (2)	1983 (3)	4060 (3)	2.9
C(2)	8353 (2)	1654 (3)	5166 (3)	3.0
C(4)	7256 (2)	2744 (3)	5828 (3)	2.7
C(4A)	6590 (2)	2127 (3)	5061 (3)	2.7
C(5)	7053 (3)	3726 (3)	6303 (4)	3.4
C(6)	6185 (3)	4129 (3)	6004 (4)	3.7
C(7)	5527 (3)	3582 (3)	5258 (3)	3.3
C(7A)	5718 (2)	2564 (3)	4783 (3)	2.5
C(8A)	5193 (2)	910 (3)	3761 (3)	2.7
C(9)	4448 (3)	344 (4)	3133 (4)	3.7
C(10)	4510 (3)	-761 (4)	2908 (4)	4.2
C(11)	5302 (3)	-1320 (4)	3327 (4)	3.7
C(12)	6039 (3)	-768 (3)	3902 (3)	3.2
C(12A)	6031 (2)	389 (3)	4087 (3)	2.3
C(13)	6790 (2)	1068 (3)	4627 (3)	2.2
C(1')	7961 (3)	-187 (3)	4154 (3)	2.7
C(2')	8232 (3)	-1164 (3)	4990 (3)	3.0
C(3')	8281 (3)	-2208 (3)	4286 (3)	3.2
C(5')	8240 (4)	-4247 (4)	4324 (5)	5.3
C(6')	9261 (3)	-3277 (4)	5877 (5)	5.1
C(1'')	8402 (3)	2409 (3)	4112 (4)	3.7
C(2'')	9256 (3)	1156 (4)	5680 (4)	3.9

Cl-atom positions derived from three-dimensional Patterson map, remaining non-hydrogen atoms from subsequent difference electron density maps, H atoms in calculated positions (C-H, N-H 0.95 \AA). F_{obs} corrected for Lorentz and polarization used for refinement of atomic positions and anisotropic temperature factors, scale factor and weighting parameter; $w = 1.071/[\sigma^2(F) + gF^2]$, $g = 6.74 \times 10^{-4}$; $R = 0.040$, $wR = 0.041$, $\Delta_{\text{max}}/\sigma = 0.094$ for positions; max. $\Delta\rho$ excursion in final difference map 0.69 e \AA^{-3} ; atomic scattering factors from *International Tables for X-ray Crystallography* (1974). Calculations performed with the Enraf-Nonius (1981) *Structure Determination Package* on a PDP-11 computer for initial data reduction and with *SHELX76* (Sheldrick, 1976), on the University of Auckland IBM 4341 computer for structure solution and refinement. Diagrams were produced using *ORTEP* (Johnson, 1965).

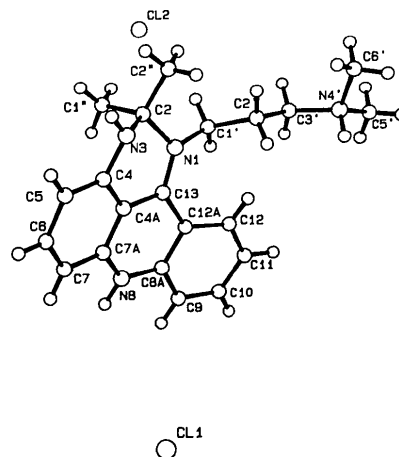


Fig. 1. Molecular geometry and atomic numbering. H atoms are numbered according to the atoms to which they are attached.

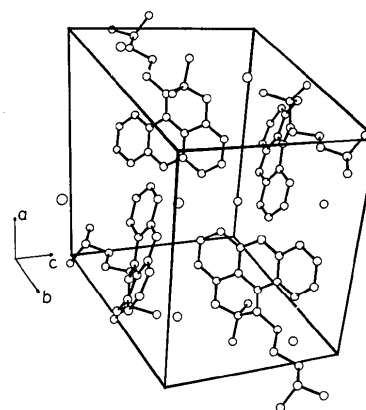


Fig. 2. A packing diagram of the unit cell.

Discussion. Atomic positions and equivalent isotropic thermal parameters are given in Table 1.* The molecular geometry and atomic numbering are depicted in Fig. 1. The unit-cell packing is shown in Fig. 2.

The X-ray analysis shows that the 1-amino-9-(dimethylaminopropyl)acridine has condensed with one mole of acetone across the primary amine function N(3) and the secondary amine function N(1) to complete a new six-membered ring. The crystals studied are the dihydrochloride, with the sites of protonation being the acridine N(8) and the side-chain N(4').

Interatomic distances and angles are listed in Table 2. Although most are normal values a few deserve comment. In particular we note that the bonds C(4)—N(3) and C(13)—N(1) are 1.369 (4) and 1.346 (4) Å, respectively, which are substantially shorter than the other bonds to these N atoms, presumably as a consequence of the reduced covalent radius of an aromatic C relative to one that is sp^3 hybridized. The only bond lengths which could be considered atypical are C(4A)—C(13), 1.433 Å, and C(12A)—C(13), 1.456 Å, which should conform to the standard aromatic-ring distance of 1.393 Å. Indeed, all other aromatic C—C bonds average 1.392 Å. A concomitant increase in the angles N(1)—C(13)—C(12A) and C(13)—C(12A)—C(12) from the expected 120° to 125.4 and 126.2°, respectively, reveals a significant buckling of the acridine-ring system near C(13) and C(12A). The only buckle possible is a distortion from planarity. Accordingly, planes of best fit were calculated through the individual rings of the acridine nucleus. Particulars of these planes have been deposited. The calculations show that the left-hand ring (of Fig. 1) is planar, the central ring is folded about a line passing through atoms N(8) and C(13) such that the dihedral angle between the two halves of the ring is 11.9°, and the right-hand ring is significantly buckled, and is twisted relative to the left-hand ring. The dihedral angle between the left- and right-hand rings is 17.5°. The extent of these deviations from planarity is shown in the edge-on view of Fig. 3. A literature search of published crystallographic studies of acridine and acridinium compounds shows that the ring systems are frequently buckled to a small extent, with a maximum dihedral angle between the outer two rings of 10°. The observed dihedral angle of 17.5° in the present compound presumably results from the steric constraints imposed upon the molecule by the cyclic condensation. Construction of a model using standard bond lengths and angles showed the molecule to be

suffering considerable strain until relieved by allowing for the observed bond lengths and angles and molecular buckling.

Table 2. Bond distances (Å) and angles (°)

N(1)—C(2)	1.514 (4)	C(4A)—C(7A)	1.413 (5)
N(1)—C(13)	1.346 (4)	C(4A)—C(13)	1.433 (5)
N(1)—C(1')	1.482 (4)	C(5)—C(6)	1.394 (5)
N(3)—C(2)	1.440 (5)	C(6)—C(7)	1.356 (5)
N(3)—C(4)	1.369 (4)	C(7)—C(7A)	1.405 (5)
N(8)—C(7A)	1.351 (4)	C(8A)—C(9)	1.400 (5)
N(8)—C(8A)	1.366 (5)	C(8A)—C(12A)	1.411 (5)
N(4')—C(3')	1.497 (4)	C(9)—C(10)	1.370 (6)
N(4')—C(5')	1.484 (5)	C(10)—C(11)	1.388 (6)
N(4')—C(6')	1.486 (5)	C(11)—C(12)	1.361 (5)
C(2)—C(1'')	1.538 (5)	C(12)—C(12A)	1.418 (5)
C(2)—C(2'')	1.515 (5)	C(12A)—C(13)	1.456 (5)
C(4)—C(4A)	1.419 (5)	C(1')—C(2')	1.530 (5)
C(4)—C(5)	1.372 (5)	C(2')—C(3')	1.513 (5)
C(2)—N(1)—C(13)	118.1 (3)	C(5)—C(6)—C(7)	122.2 (4)
C(2)—N(1)—C(1')	115.3 (3)	C(6)—C(7)—C(7A)	119.3 (4)
C(13)—N(1)—C(1')	124.2 (3)	N(8)—C(7A)—C(4A)	118.8 (3)
C(2)—N(3)—C(4)	116.4 (3)	N(8)—C(7A)—C(7)	120.8 (3)
C(7A)—N(8)—C(8A)	122.1 (3)	C(4A)—C(7A)—C(7)	120.3 (4)
C(3')—N(4')—C(5')	111.9 (3)	N(8)—C(8A)—C(9)	117.3 (4)
C(3')—N(4')—C(6')	112.7 (3)	N(8)—C(8A)—C(12A)	121.4 (3)
C(5')—N(4')—C(6')	109.5 (4)	C(9)—C(8A)—C(12A)	121.3 (4)
N(1)—C(2)—N(3)	107.5 (3)	C(8A)—C(9)—C(10)	119.7 (4)
N(1)—C(2)—C(1'')	107.5 (3)	C(9)—C(10)—C(11)	120.0 (4)
N(1)—C(2)—C(2'')	112.5 (3)	C(10)—C(11)—C(12)	120.6 (4)
N(3)—C(2)—C(1'')	111.3 (3)	C(11)—C(12)—C(12A)	121.7 (4)
N(3)—C(2)—C(2'')	107.2 (3)	C(8A)—C(12A)—C(12)	116.0 (4)
C(1'')—C(2)—C(2'')	110.8 (3)	C(8A)—C(12A)—C(13)	117.7 (3)
N(3)—C(4)—C(5)	123.7 (3)	C(12)—C(12A)—C(13)	126.2 (3)
N(3)—C(4)—C(4A)	115.4 (3)	N(1)—C(13)—C(4A)	118.2 (3)
C(4A)—C(4)—C(5)	120.8 (3)	N(1)—C(13)—C(12A)	125.4 (3)
C(4)—C(4A)—C(7A)	118.0 (3)	C(4A)—C(13)—C(12A)	116.4 (3)
C(4)—C(4A)—C(13)	120.7 (3)	N(1)—C(1')—C(2')	113.5 (3)
C(7A)—C(4A)—C(13)	121.2 (3)	C(1')—C(2')—C(3')	110.1 (3)
C(4)—C(5)—C(6)	119.3 (4)	N(4')—C(3')—C(2')	112.4 (3)

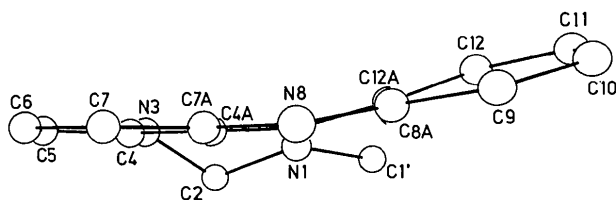


Fig. 3. An edge-on view of the acridine-ring system.

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* Lists of anisotropic thermal parameters, H-atom positions, least-squares planes and observed and calculated structure factor amplitudes have been deposited with the British Library Lending Division as Supplementary Publication No. SUP 42705 (14 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.