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Nucleic Acid Intercalating Drug. The Structure of 9-Hydroxy-2,5,6,11-tetramethylpyrido[4,3-*b*]carbazolium (9-Hydroxy-2,6-dimethylellipticinium) Chloride Monohydrate

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Abstract. $C_{19}H_{19}N_2O^+.Cl^-.H_2O$, $M_r = 344{\cdot}6$, triclinic, $P\bar{1}$, $a = 12{\cdot}980$ (1), $b = 9{\cdot}454$ (2), $c = 7{\cdot}148$ (1) Å, $\alpha = 75{\cdot}23$ (2), $\beta = 99{\cdot}73$ (3), $\gamma = 91{\cdot}83$ (2)°, $V = 835{\cdot}9$ Å^3, $Z = 2$, $D_m = 1{\cdot}35$ (2), $D_x = 1{\cdot}369$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 2{\cdot}11$ mm^{-1}, $F(000) = 364$, $T = 298$ K, $R = 0{\cdot}059$ for 2767 observed reflections. Antitumour drug that displays one of the highest DNA affinities ($4 \times 10^6\ M^{-1}$) among ellipticine derivatives. The structure analysis confirms the intercalation hypothesis. There is stacking of centrosymmetrically related parallel molecules along **c**, alternately spaced by 3·43 and 3·48 Å. The crystal structure confirms the desolvation effect of the sixth nitrogen position.

Introduction. Drugs in the ellipticine series have antitumour properties toward several experimental tumours (Dalton, Demerac, Elmes, Loder, Swan & Teitei, 1967); this has been related to their intercalation into DNA base pairs (Le Pecq, Dat-Xuong, Gosse & Paoletti, 1974; Jain, Bhandary & Sobell, 1979). We have already pointed out the role of various substituents on the basic ellipticine molecule in increasing both DNA affinity and antitumour efficiency. The title compound (Fig. 1*a*) possesses pharmacological properties similar to those of its direct derivative 9-hydroxy-2-methylellipticinium (celiptium) (Le Pecq, Gosse, Dat-Xuong & Paoletti, 1975), the structure of which is described in the preceding paper (Salahou, Courseille & Tsai, 1988). The methylation of nitrogen in position 6 gives a threefold increase of DNA affinity (Paoletti, Cros, Dat-Xuong, Lecointe & Moisand, 1979). It is assumed that a water molecule attached by a hydrogen bond to position 6 would be expelled from the DNA helix when the compound intercalates in DNA. As a consequence of this dehydration, the binding free energy would be decreased because of the loss of the solvation energy. When the molecule is methylated at this position, this effect would no longer be present and the DNA binding free energy would, therefore, be larger as observed.

In order to discover whether methylation has an effect on the conformation of the ellipticinium ring, it is clear that a comparative structural study of the two derivatives must be carried out.

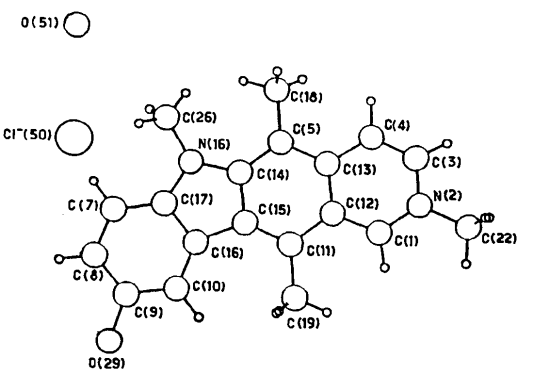

Fig. 1. View of the molecule with atomic numbering.

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Experimental. The compound was provided by Dr Dat-Xuong; small crystals were obtained from DMF solution by slow evaporation; crystal dimensions (mm): 0·41 × 0·26 × 0·08; D_m by flotation; cell dimensions from angular measurements of 25 strong reflections in the range $\theta < 20°$; Enraf–Nonius CAD-4 diffractometer, graphite-monochromated Cu $K\alpha$ radiation; ω–θ scan; $\theta_{max} = 55°$; $-15 < h < 15$; $-11 < k < 11$; $0 < l < 8$; two standard reflections with constant intensity; 3037 measured reflections with 2767 observed [$I > 3\sigma(I)$]; data corrected for Lorentz and polarization but not for absorption; structure by Patterson method and Fourier difference maps; refinement by block-diagonal methods; H atoms localized from a $\Delta\rho$ map; all positional parameters were refined; anisotropic thermal parameters of all non-hydrogen atoms and isotropic thermal parameters of all H atoms; the function $\sum w(F_o - F_c)^2$ was minimized with $w = 1$ if $F_o < p$ and $w = p^2/F_o^2$ if $F_o > p$, where $p = (F^2_{o,max}/10)^{1/2}$; maximum height in final difference Fourier map 0·5 e Å^{-3}; $(\Delta/\sigma)_{max}$ for x, y, z of non-H atoms 0·57; $R = 0·059$; $wR = 0·061$; $S = 0·82$; atomic scattering factors from *International Tables for X-ray Crystallography* (Cromer & Waber, 1974).

Discussion. Atomic positional parameters and equivalent isotropic thermal parameters are listed in Table 1.* By comparison with its direct derivative, the bond lengths (Table 2) differ by no more than 0·009 Å. Only three bonds display a difference of about 0·015 Å: C(8)–C(9), C(9)–O(29) and C(16)–C(17). The valence angles are generally in agreement with their corresponding values. However, a difference ($\delta = 2·1°$) for the C(5)–C(14)–C(6) angle is noteworthy; this can be related to the effect of the methylation in position 6. Nevertheless, the addition of the methyl group does not affect the planarity of the ring systems, since the deviations of the atoms from the mean molecular plane range from 0·07 Å for N(2) to −0·08 Å for C(5). For the atoms located out of the four rings, we observe a significant deviation, which is not unexpected: δC(18) = −0·32, δC(19) = −0·05, δO(29) = −0·13, δC(22) = −1·93, δC(26) = +0·36 Å. The deviation from the mean plane of the adjacent methyl groups C(18) and C(26) results from mutual steric hindrance. These structural parameters are similar to those reported in parent ellipticines (Courseille, Busetta & Hospital, 1974, 1982; Courseille, Busetta & Precigoux, 1981; Garlich, Kaiser & Schlemper, 1984).

Table 1. *Atomic coordinates and equivalent isotropic thermal parameters* (Å^2)

$B_{eq} = \frac{4}{3}\sum_i\sum_j \beta_{ij}\mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	B_{eq}
C(1)	0·2152 (2)	0·4189 (3)	0·2527 (4)	3·2
N(2)	0·1440 (2)	0·3136 (3)	0·2576 (3)	3·7
C(3)	0·1707 (2)	0·1751 (3)	0·2569 (4)	4·0
C(4)	0·2702 (2)	0·1416 (3)	0·2517 (4)	3·7
C(5)	0·4566 (2)	0·2117 (2)	0·2530 (3)	2·8
N(6)	0·6357 (1)	0·3208 (2)	0·2751 (3)	2·9
C(7)	0·7758 (2)	0·5089 (3)	0·2723 (4)	3·3
C(8)	0·7951 (2)	0·6566 (3)	0·2554 (4)	3·2
C(9)	0·7137 (2)	0·7536 (3)	0·2389 (4)	3·0
C(10)	0·6119 (2)	0·7054 (2)	0·2402 (3)	2·7
C(11)	0·3942 (2)	0·5075 (2)	0·2436 (3)	2·7
C(12)	0·3202 (2)	0·3915 (2)	0·2500 (3)	2·7
C(13)	0·3518 (2)	0·2468 (2)	0·2525 (3)	2·8
C(14)	0·5286 (2)	0·3232 (2)	0·2633 (3)	2·7
C(15)	0·4969 (2)	0·4706 (2)	0·2522 (3)	2·4
C(16)	0·5910 (2)	0·5575 (2)	0·2520 (3)	2·5
C(17)	0·6735 (2)	0·4618 (2)	0·2676 (3)	2·6
C(18)	0·4836 (2)	0·0645 (3)	0·2275 (4)	3·7
C(19)	0·3628 (2)	0·6621 (3)	0·2286 (4)	3·2
C(22)	0·0348 (2)	0·3455 (4)	0·2688 (5)	5·0
C(26)	0·7074 (2)	0·1969 (3)	0·3295 (5)	4·1
O(29)	0·7290 (1)	0·9000 (2)	0·2200 (3)	4·0
Cl(50)	0·9170 (1)	0·2370 (1)	0·7867 (1)	5·6
O(51)	0·9194 (2)	0·0035 (2)	0·1904 (4)	5·5

Table 2. *Bond lengths* (Å, $\bar{\sigma} \simeq 0·005$ Å) *and valence angles* (°, $\bar{\sigma} \simeq 0·3°$)

C(1)–N(2)	1·334	C(14)–C(15)	1·445
N(2)–C(3)	1·367	C(15)–C(16)	1·450
N(2)–C(22)	1·478	C(16)–C(17)	1·396
C(3)–C(4)	1·349	C(17)–N(6)	1·397
C(4)–C(13)	1·430	C(14)–N(6)	1·379
C(13)–C(12)	1·436	N(6)–C(26)	1·451
C(12)–C(1)	1·400	C(7)–C(17)	1·385
C(12)–C(11)	1·432	C(7)–C(8)	1·389
C(13)–C(5)	1·410	C(8)–C(9)	1·391
C(5)–C(18)	1·508	C(9)–O(29)	1·367
C(5)–C(14)	1·394	C(9)–C(10)	1·385
C(11)–C(19)	1·502	C(10)–C(16)	1·400
C(11)–C(15)	1·376		

C(12)–C(1)–N(2)	121·4	C(8)–C(9)–O(29)	122·5
C(1)–N(2)–C(22)	119·7	C(8)–C(9)–C(10)	120·9
C(1)–C(2)–C(3)	121·1	C(10)–C(9)–O(29)	116·5
C(22)–N(2)–C(3)	119·0	C(9)–C(10)–C(16)	119·0
N(2)–C(3)–C(4)	120·5	C(1)–C(12)–C(13)	119·1
C(3)–C(4)–C(13)	121·8	C(1)–C(12)–C(11)	119·8
C(4)–C(13)–C(12)	115·8	C(13)–C(12)–C(11)	120·1
C(5)–C(13)–C(4)	122·2	C(12)–C(11)–C(19)	122·4
C(5)–C(13)–C(12)	121·8	C(12)–C(11)–C(15)	116·5
C(13)–C(5)–C(14)	116·1	C(15)–C(11)–C(19)	121·0
C(18)–C(5)–C(13)	119·8	C(26)–N(6)–C(17)	120·3
C(14)–C(5)–C(18)	123·9	N(6)–C(17)–C(7)	128·1
C(5)–C(14)–N(6)	129·6	C(7)–C(17)–C(16)	121·8
N(6)–C(14)–C(15)	108·0	N(6)–C(17)–C(16)	110·0
C(5)–C(14)–C(15)	122·2	C(17)–C(16)–C(10)	119·2
C(14)–C(15)–C(11)	121·9	C(17)–C(16)–C(15)	106·4
C(16)–C(15)–C(11)	131·4	C(10)–C(16)–C(15)	134·5
C(14)–C(15)–C(16)	106·6	C(17)–C(7)–C(8)	118·3
C(14)–N(6)–C(26)	129·5	C(7)–C(8)–C(9)	120·6
C(14)–N(6)–C(17)	108·8		

The molecules related by centres of symmetry are stacked face-to-face to make a columnar structure along the c axis (Fig. 2).

The distance between these overlapping molecular planes is alternately 3·43 and 3·48 Å. They are

* Lists of structure factors, anisotropic thermal parameters and H-atom parameters have been deposited with the British Library Document Supply Centre as Supplementary Publication No. SUP 51113 (23 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

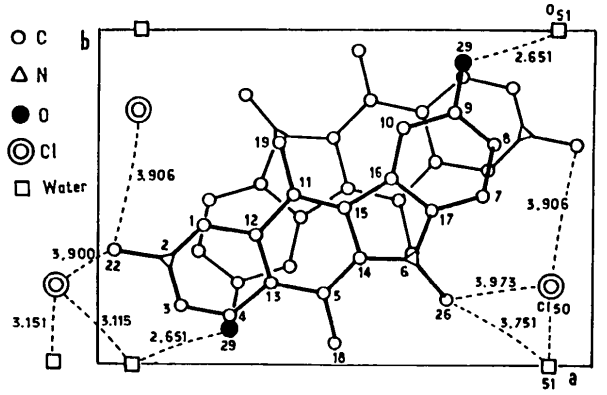

Fig. 2. Projection of the structure along the *c* axis.

connected *via* hydrogen bonds involving the hydroxyl group, chloride ions and water molecule as follows: O(29)—H(x, y, z)···O(51)(x, $1+y$, z) = 2·651 (6) Å; O(51)—H(x, y, z)···Cl$^-$(50)(2−x, −y, 1−z) = 3·115 (5) Å; and O(51)—H(x, y, z)···Cl$^-$(50)(x, y, −1+z) = 3·151 (5) Å (hydrogen atoms have not been found in the difference Fourier maps). The remaining intermolecular contacts are in the range of van der Waals interactions.

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Composé Moléculaire Acide L-Malique–L-Citrulline (1/1)

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(*Reçu le* 1 *mars* 1988, *accepté le* 4 *juillet* 1988)

Abstract. $C_4H_6O_5.C_6H_{13}N_3O_3$, $M_r = 309·3$, monoclinic, $P2_1$, $a = 8·934$ (3), $b = 5·368$ (1), $c = 14·377$ (4) Å, $\beta = 91·96$ (3)°, $V = 689·1$ (6) Å^3, $Z = 2$, $D_x = 1·490$ Mg m^{-3}, Mo $K\bar{\alpha}$, $\lambda = 0·7107$ Å, $\mu = 0·12$ mm^{-1}, $F(000) = 328$, $T = 294$ (1) K, $R = 0·039$ for 1169 independent reflections. The L-citrulline molecule is zwitterionic. Its geometry does not show very significant deviations from that of the same molecule in L-citrulline or L-citrulline dihydrate. The carbon chain of the L-malic acid molecule is planar and displays an antiperiplanar conformation. Bond lengths and angles agree with published values for the β modification of (DL)-malic acid. The structure is constituted of layers of L-citrulline molecules which alternate with layers of L-malic acid molecules. These layers spread out along the $z = 0$ and $z = \frac{1}{2}$ planes, respectively. Numerous N—H···O and O—H···O hydrogen bonds link the molecules together.

Introduction. L'exploration, par analyse thermique, du système acide L(−)-malique–L(+)-citrulline (Céolin, Toffoli, Khodadad, Lepage & Astoin, 1986), a permis d'envisager l'existence d'un composé péritectique de stoechiométrie 1:1. L'étude structurale de ce composé a

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