e.g. C(10) perpendicular to the plane of the ring shows a peanut shape (Fig. 3). From the anisotropic temperature parameters we enumerated a librational amplitude of 48°, a value which agrees well with the value inferred from the observed shrinkage of the bond lengths involved. C(9)C(10) and C(9)C(11) are apparently shrunk by 0·023 Å, when compared with the normal aromatic CC distance (1·391 Å, average over the outer ring). This corresponds to an average rotation of arccos (1·366/1·391) = 10·8° in the positive and negative direction; hence the half-rotational angle is estimated as 22°, and the full angle as 43°. Also the librational motion will apparently decrease C(10)C(9)C(11) and increase C(9)C(10)C(11*B*).

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Structure of an Antitumour Drug: 9-Hydroxy-2,5,11-trimethyl-6*H*-pyrido[4,3-*b*]-carbazolium Acetate (9-Hydroxy-2-methylellipticinium Acetate; Celiptium®) Dihydrate

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Abstract. $C_{18}H_{17}N_2O^+.C_2H_3O_2^-.2H_2O$, $M_r = 336{\cdot}2$, monoclinic, $C2/c$, $a = 21{\cdot}789\ (2)$, $b = 12{\cdot}853\ (1)$, $c = 14{\cdot}004\ (2)$ Å, $\beta = 114{\cdot}80\ (1)°$, $V = 3560{\cdot}2$ Å^3, $Z = 8$, $D_m = 1{\cdot}24$, $D_x = 1{\cdot}255$ Mg m^{-3}, λ(Cu $K\alpha$) = 1·54178 Å, $\mu = 0{\cdot}754$ mm^{-1}, $F(000) = 1584$, $T = 298$ K, $R = 0{\cdot}052$ for 2236 observed reflections. Antitumour drug. The crystal structure involves the packing of resonant rings held together by a network of hydrogen bonds involving hydroxyl groups, acetate ions and water molecules. The main feature is the two stacking patterns found together in the crystal structure; this feature appears to differ from other derivatives.

Introduction. Ellipticine (5,11-dimethyl-6*H*-pyrido[4,3-*b*]carbazole) is a plant alkaloid of the Apocynacae family that possesses pharmacological activity. Many of its derivatives have been synthesized (Dalton, Demerac, Elmes, Leder, Swan & Teitei, 1967; Le Pecq, Dat-Xuong, Gosse & Paoletti, 1974). A study of the mechanism of the antitumour action of these substances established that most intercalate into DNA base pairs (Festy, Poisson & Paoletti, 1971). The search for new derivatives with stronger affinity for DNA led to the synthesis of new ellipticine derivatives (Le Pecq, Gosse, Dat-Xuong & Paoletti, 1975). One of these, the title compound (Fig. 1*a*), gives remarkable results in clinical tests (Juret, Tanguy, Le Talaer, Abbatucci, Dat-Xuong, Le Pecq & Paoletti, 1978). This compound, 'celiptium', is a commercial drug from the Sanofi company. Both the 9-hydroxylation and the quaternarization of the 2-pyridine nitrogen of ellipticine that yield this derivative tend to increase DNA binding and antitumour activity.

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It is therefore of interest to study the structure of 9-hydroxy-2-methylellipticinium in order to analyse the different types of interactions (crystal packing, hydrogen bonding, ...) that play an important role in its DNA affinity and, consequently, stabilize the complex during the intercalation process.

Experimental. The compound was a gift from Sanofi; orange plate-like crystals grown at room temperature from DMF solution were mounted in mother liquor; D_m by flotation; a crystal $0.57 \times 0.15 \times 0.075$ mm was used for data collection on an Enraf–Nonius CAD-4 diffractometer with Cu $K\alpha$ radiation ($\lambda = 1.5418$ Å), graphite monochromator; least-squares regression analysis of 25 reflections yielded cell dimensions; ω–θ scan mode; 2526 reflections measured; $\theta_{max} = 60°$; two standard reflections, $\bar{3}14$ and $\bar{2}04$, measured periodically showed no decrease of intensities; $-22 \le h_{max} \le 22$, $0 \le k_{max} \le 13$ and $0 \le l_{max} \le 14$; data corrected for Lp; no absorption correction; a total of 2236 observed reflections with $I > 3\sigma(I)$; direct methods, program *MULTAN*80 (Main, Fiske, Hull, Lessinger, Germain, Declercq & Woolfson, 1980); refinement with isotropic and anisotropic temperature parameters for all non-H atoms using block-diagonal methods, H atoms introduced with their computed coordinates; minimization of $\sum w(|F_o| - |F_c|)^2$ with $w = 1$ if $F_o < p$ and $w = p^2/F_o^2$ if $F_o > p$, where $p = (F^2_{o,max}/10)^{1/2}$; scattering factors of Cromer & Waber (1974) for non-H atoms; Stewart, Davidson & Simpson (1965) for H atoms; residual electron density $\Delta\rho = 0.4$ e Å^{-3}, final $R = 0.052$, $wR = 0.059$, $S = 0.77$, $(\Delta/\sigma)_{max}$ for x, y, z of C,N,O $= 0.2$. The positional and thermal parameters of all non-H atoms appear in Table 1.*

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)	0·1226 (2)	0·6402 (3)	0·2062 (3)	3·0
N(2)	0·1880 (1)	0·6167 (2)	0·2537 (2)	3·3
C(3)	0·2092 (2)	0·5151 (3)	0·2755 (3)	3·6
C(4)	0·1633 (2)	0·4372 (3)	0·2466 (3)	3·5
C(5)	0·0458 (2)	0·3760 (3)	0·1612 (3)	2·9
N(6)	−0·0772 (2)	0·3429 (2)	0·0687 (2)	3·3
C(7)	−0·2021 (2)	0·3712 (3)	−0·0195 (3)	3·6
C(8)	−0·2521 (2)	0·4461 (3)	−0·0493 (3)	3·8
C(9)	−0·2356 (2)	0·5521 (3)	−0·0313 (3)	3·5
C(0)	−0·1686 (2)	0·5846 (3)	0·0155 (3)	3·1
C(11)	0·0026 (2)	0·5925 (3)	0·1264 (3)	2·7
C(12)	0·0722 (2)	0·5647 (3)	0·1749 (3)	2·6
C(13)	0·0927 (2)	0·4572 (3)	0·1935 (3)	2·8
C(14)	−0·0216 (2)	0·4061 (3)	0·1109 (3)	2·8
C(15)	−0·0435 (2)	0·5127 (3)	0·0964 (3)	2·5
C(16)	−0·1171 (2)	0·5099 (3)	0·0460 (3)	2·7
C(17)	−0·1351 (2)	0·4040 (3)	0·0292 (3)	3·0
C(18)	0·0660 (2)	0·2633 (3)	0·1799 (3)	4·2
C(19)	−0·0192 (2)	0·7043 (3)	0·1074 (3)	4·0
C(22)	0·2400 (2)	0·6992 (3)	0·2860 (3)	4·5
O(29)	−0·2853 (1)	0·6272 (2)	−0·0566 (2)	4·6
C(30)	0·0878 (2)	−0·0331 (3)	0·5177 (3)	5·1
C(31)	0·1014 (2)	0·0820 (3)	0·5145 (3)	3·8
O(32)	0·0788 (1)	0·1261 (2)	0·4259 (2)	4·6
O(33)	0·1351 (2)	0·1279 (2)	0·5998 (2)	5·7
O(50)	0·3914 (1)	0·4014 (3)	0·2339 (2)	6·2
O(51)	0·5000	0·5211 (3)	0·2500	4·5

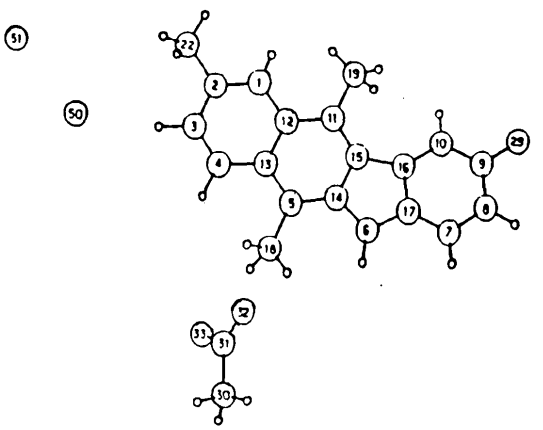

Fig. 1 View of the molecule with atomic numbering.

Table 2. *Bond lengths* (Å, $\bar{\sigma} \simeq 0.005$ Å) *and valence angles* (°, $\bar{\sigma} \simeq 0.4°$)

C(1)–N(2)	1·332	C(15)–C(16)	1·460
N(2)–C(3)	1·373	C(16)–C(17)	1·411
N(2)–C(22)	1·481	N(6)–C(17)	1·389
C(3)–C(4)	1·350	N(6)–C(14)	1·368
C(4)–C(13)	1·422	C(7)–C(17)	1·390
C(12)–C(13)	1·441	C(7)–C(8)	1·380
C(12)–C(1)	1·390	C(8)–C(9)	1·407
C(12)–C(11)	1·423	C(9)–C(10)	1·393
C(11)–C(15)	1·373	C(10)–C(16)	1·402
C(14)–C(15)	1·438	C(9)–O(29)	1·381
C(5)–C(14)	1·392	C(30)–C(31)	1·523
C(5)–C(13)	1·396	C(31)–O(32)	1·262
C(11)–C(19)	1·499	C(31)–O(33)	1·258
C(5)–C(18)	1·506		

C(12)–C(1)–N(2)	122·6	N(6)–C(14)–C(15)	109·1
C(1)–N(2)–C(3)	120·9	C(14)–C(15)–C(11)	121·0
C(1)–N(2)–O(22)	120·9	C(14)–C(15)–C(16)	105·9
C(3)–N(2)–O(22)	118·2	C(11)–C(15)–C(16)	133·1
N(2)–C(3)–C(4)	120·1	C(14)–N(6)–C(17)	109·2
C(3)–C(4)–C(13)	121·6	N(6)–C(17)–C(16)	109·6
C(5)–C(13)–C(4)	121·2	N(6)–C(17)–C(7)	128·1
C(5)–C(13)–C(12)	121·9	C(7)–C(17)–C(16)	118·9
C(4)–C(13)–C(12)	116·9	C(17)–C(16)–C(10)	118·9
C(13)–C(12)–C(1)	117·9	C(17)–C(16)–C(15)	106·2
C(13)–C(12)–C(11)	121·1	C(10)–C(16)–C(15)	134·9
C(1)–C(12)–C(11)	121·0	C(17)–C(7)–C(8)	118·2
C(12)–C(11)–C(15)	116·9	C(7)–C(8)–C(9)	120·7
C(15)–C(11)–C(19)	121·4	C(8)–C(9)–O(29)	121·4
C(12)–C(11)–C(19)	121·6	C(8)–C(9)–C(10)	121·0
C(13)–C(5)–C(14)	115·5	C(10)–C(9)–O(29)	117·6
C(13)–C(5)–C(18)	122·8	C(9)–C(10)–C(16)	118·9
C(14)–C(5)–C(18)	121·7	C(30)–C(31)–O(32)	118·1
C(5)–C(14)–C(15)	123·5	C(30)–C(31)–O(33)	117·9
C(5)–C(14)–N(6)	127·5	O(32)–C(31)–O(33)	124·0

* 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 51110 (16 pp.). Copies may be obtained through The Executive Secretary, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

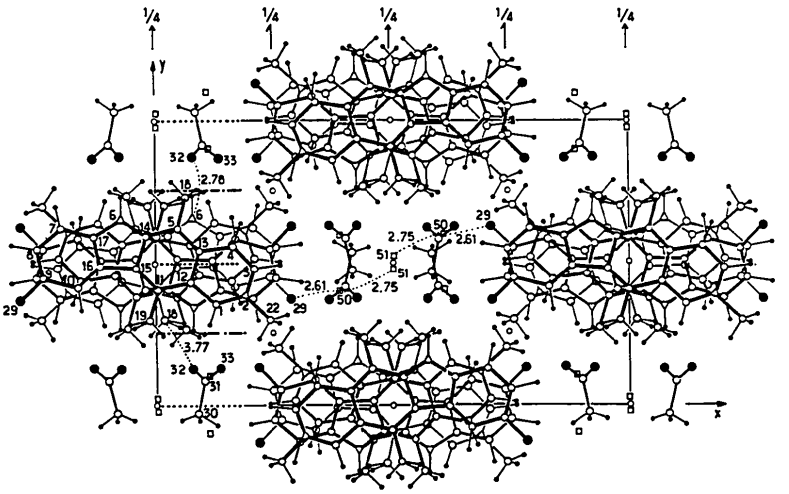

Fig. 2. Projection of the structure along the *c* axis.

Discussion. As can be seen from Table 2, bond lengths and valence angles are close to those observed in the ellipticine molecule determined previously (Courseille, Busetta & Hospital, 1974, 1982) with the exception of one bond and three angles which exhibit significant deviations: C(1)–C(12) ($\delta = 0{\cdot}03$ Å), N(2)–C(1)–C(12) ($\delta = 3{\cdot}4°$), C(1)–N(2)–C(3) ($\delta = 3{\cdot}8°$), N(2)–C(3)–C(4) ($\delta = 3°$). These differences are due to the cationic form of this molecule.

Therefore, the quaternarization of the 2-pyridine nitrogen by the methyl group and the substitution of the 9 position by the hydroxyl group have very little influence on the conformation of the molecule and affect only very slightly the planarity of the ellipticinium ring: the maximum deviation from the least-squares plane is 0·009 Å. The methyl group in position 2 has a deviation $\delta C(22) = -0{\cdot}10$ Å whereas those in positions 5 and 11 deviate $\delta C(18) = +0{\cdot}12$ and $\delta C(19) = +0{\cdot}21$ Å, respectively.

A projection of the structure is shown in Fig. 2; molecules stack on one another along the *c* axis with their planes parallel. The main characteristic of this compound is that we observe at the same time the two stacking patterns usually found in the crystal structures of ellipticine derivatives. Here, 9-hydroxy-2-methylellipticinium is respectively stacked above and below by a centrosymmetric homologue and by a translated homologue related by the glide plane. The stacked molecules are therefore alternately separated by distances of 3·44 to 3·53 Å and exhibit high overlaps of aromatic rings.

The cohesion of the layers formed is assured by hydrogen bonds (Table 3) involving hydroxyl groups, acetate ions and water molecules. In addition to hydrogen bonds, van der Waals contacts reinforce intermolecular contacts.

Table 3. *Hydrogen bonds*

Donor (*D*)–H	Acceptor (*A*)	*D*···*A* (Å)	Angle *D*–H···*A* (°)
N(6)–H(106) |*x*, *y*, *z*|	O(32) |$-x, +y, \frac{1}{2}-z$|	2·789 (5)	178 (4)
O(29)–H* |*x*, *y*, *z*|	O(50) |$-x, 1-y, -z$|	2·614 (5)	
O(50) |*x*, *y*, *z*|	O(33) |$\frac{1}{2}-x, \frac{1}{2}-y, 1-z$|	2·652 (5)	
O(50)–H* |*x*, *y*, *z*|	O(51) |$1-x, y, \frac{1}{2}-z$|	2·751 (5)	
O(51)–H* |*x*, *y*, *z*|	O(32) |$\frac{1}{2}+x, \frac{1}{2}+y, +z$|	2·699 (5)	
O(51)–H* |*x*, *y*, *z*|	O(32) |$\frac{1}{2}-x, \frac{1}{2}+y, \frac{1}{2}-z$|	2·699 (5)	

* Hydrogen atoms not located in the Fourier difference maps.

This structure shows the importance of substituents on ellipticine. The positive charge on N(2) is delocalized over the pyridine ring since it does not appear explicitly in the crystal structure. Meanwhile we observe that the hydroxyl group can be involved in hydrogen bonds, during the intercalation, with the phosphate–sugar chains; this reinforces the DNA affinity. This work is a preparatory study for the structural determination of the complex between this compound and DNA fragments.

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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.

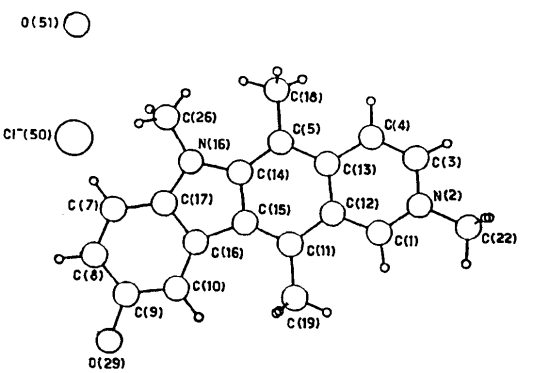

Fig. 1. View of the molecule with atomic numbering.

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