inversion centers, thus producing a zigzag pattern along the [10$\bar{1}$] direction. Comparison of the unit-cell dimensions and packing arrangements for 2,3-NDC to those of *o*-phthalic acid (Ermer, 1981; Küppers, 1981) shows very close agreement in most details, excepting the *b* cell-edge lengths: 19.222 (3) Å for 2,3-NDC; 14.287 (3) Å for phthalic acid. In the present case, the length of the additional aromatic ring is accommodated by the larger *b* cell edge.

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Structure of 9-Epiquinine Hydrochloride Dihydrate *versus* Antimalarial Activity

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Abstract. 9-Epiquinine hydrochloride dihydrate [(9*S*)-6′-methoxycinchonan-9-ol hydrochloride dihydrate], $C_{20}H_{25}N_2O_2^+.Cl^-.2H_2O$, $M_r = 396.9$, orthorhombic, $P2_12_12_1$, $a = 8.059$ (2), $b = 11.537$ (3), $c = 22.311$ (6) Å, $V = 2074.1$ (9) Å^3, $Z = 4$, $D_x = 1.271$ g cm^{-3}, Cu $K\alpha$, $\lambda = 1.54178$ Å, $\mu = 18.58$ cm^{-1}, $F(000) = 848$, room temperature, final $R = 6.56\%$ for 1344 reflections with $|F_o| > 3\sigma(F)$. 9-Epiquinine crystallized as a hydrated tertiary amine hydrochloride salt. The intramolecular N(1)$^+$···O distance is 2.816 Å. All H atoms attached to O or N atoms form intermolecular hydrogen bonds. The Cl ion is involved in four hydrogen bonds including one with the hydroxyl group of 9-epiquinine. The N(1)$^+$—H moiety hydrogen bonds to a water molecule. The O(12)—C(9)···N(1)$^+$—H(1) torsion angle was equal to -0.2 (3.8)° in comparison to 97.0° for quinidine sulfate [Karle & Karle (1981). *Proc. Natl Acad. Sci. USA*, **78**, 5938–5941]. Two theories have been proposed in the literature to explain the low antimalarial activity of 9-epiquinine. The crystal structure of 9-epiquinine hydrochloride is not consistent with the hypothesis that 9-epiquinine prefers to form intramolecular rather than intermolecular hydrogen bonds, but is consistent with the hypothesis that N(1) and the hydroxyl group of 9-epiquinine are in an orientation which is unfavorable towards exerting antimalarial activity.

Introduction. 9-Epiquinine is the epimer of the *erythro* antimalarial agents quinine and quinidine (Fig. 1). An *erythro* compound is a compound

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containing adjacent chiral centers with either an *R,S* or an *S,R* configuration, and a *threo* compound is a compound containing adjacent chiral centers with either an *R,R* or an *S,S* configuration. The conformation of 9-epiquinine is (8*S*,9*S*), of quinine is (8*S*,9*R*), and of quinidine is (8*R*,9*S*). 9-Epiquinine and 9-epiquinidine, both naturally occurring *threo* cinchona alkaloids, demonstrated minimal antimalarial activity in avian malaria assays conducted in the 1930's and 1940's (Buttle, Henry, Solomon, Trevan & Gibbs, 1938; Sweeney & Strube, 1979). Since then, the epi cinchona alkaloids have been labeled inactive as antimalarial agents. We have determined the three-dimensional structure of 9-epiquinine hydrochloride dihydrate to provide more structural information as to why the *threo* cinchona alkaloids are inactive with the hope that this information will help to decipher the mechanism of activity of the cinchona alkaloids and aid the design of active antimalarial agents.

Although the precise mechanism of action of the amino alcohol antimalarials has not been elucidated, antimalarial activity of the amino alcohol antimalarial agents appears dependent upon the ability of both the hydroxyl and the amine group to form hydrogen bonds with critical cellular constituents.

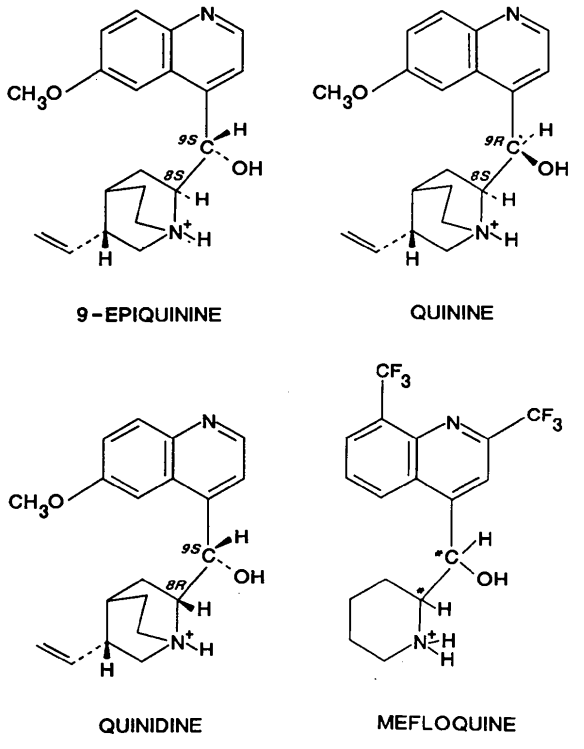

Fig. 1. Chemical structure of 9-epiquinine, quinine, quinidine and mefloquine in salt form. Mefloquine is a racemic mixture of the *R,S* and *S,R* configurations at the C atoms indicated with asterisks.

Studies with the antimalarial agent mefloquine (tradename Lariam) (Fig. 1) have shown that mefloquine loses antimalarial activity if both the amine and hydroxyl groups are acetylated, if the hydroxyl group is converted to an *O*-methyl or *O*-ethyl, or if the saturated 2-piperidyl group is unsaturated to form a 2-pyridyl group (Sweeney, 1981). Recent reviews have proposed that quinine, quinidine and mefloquine exert their antimalarial action by causing the pH of the parasitic acid vesicles to rise and, thereby, disrupting the digestive activity of these organelles (Schlesinger, Krogstad & Herwaldt, 1988; Panisko & Keystone, 1990). The pH rise observed in these organelles cannot be accounted for solely by the base activity of the cinchona alkaloids and of mefloquine since these compounds are relatively weak bases at physiological pH and since mefloquine raises vesicular pH at low nanomolar concentrations.

Two hypotheses concerning the inactivity of the 8,9-*threo* cinchona alkaloids have appeared in the literature. Oleksyn (1982) noted that the hydroxyl and amine groups of crystalline 10-bromo-10,11-dihydro-9-epiquinidine formed only an intramolecular hydrogen bond, whereas the active 8,9-*erythro* cinchona alkaloids all form intermolecular hydrogen bonds. She hypothesized that the formation of intramolecular hydrogen bonds by the epi alkaloids make their hydroxyl and amine groups inaccessible for forming intermolecular hydrogen bonds to cellular constituents critical to antimalarial activity. Alternatively, Sweeney (1981) noted that even though the 8,9-*threo* cinchona alkaloids are inactive, the *erythro* mefloquine and its *threo* isomer are both highly active antimalarial agents. He hypothesized that the more flexible piperidine ring system of mefloquine would allow positioning of the piperidine N atom in a favorable position relative to the orientation of the hydroxyl group in both the *erythro* and *threo* isomers, and that the rigid bicyclo ring system of the cinchona alkaloids prevents a favorable orientation of the hydroxyl group and the quinuclidine N atom in the *threo* epi alkaloids.

The crystal structure of epiquinine hydrochloride dihydrate described here contains only intermolecular hydrogen bonds. No intramolecular hydrogen bond between the hydroxyl group and the quinuclidine N atom was observed. The preference for epiquinine to form intermolecular hydrogen bonds appears to rule out the first hypothesis. The crystal structure of the title compound is consistent with the hypothesis that the relative orientation of the hydroxyl and amine groups is critical to antimalarial activity.

Experimental. 9-Epiquinine hydrochloride dihydrate was a generous gift from Professor K. Barry

Sharpless, Department of Chemistry, Massachusetts Institute of Technology. Diffraction data were collected from a colorless prism, 0.56 × 0.16 × 0.10 mm, in the θ–2θ mode to a maximum 2θ value of 112° on a *R3m*/micro Nicolet four-circle diffractometer (Siemens Analytical X-ray Instruments, Inc., Madison, WI) with a graphite monochromator. Range of indices: h −9→0, k 0→13 and l 0→24. A total of 1665 data were collected of which 54 data represented standard reflections. The number of unique reflections was 1589. The standard reflections 200, 040 and 004 were monitored after every 100 intensity measurements. The standards varied by up to 1.6%. The lattice parameters were based on 25 centered reflections with 2θ values between 31 and 42°. No corrections for absorption or extinction were used. The structure was solved routinely by direct phase determination (Karle & Karle, 1966). All of the non-H atoms except for the two vinyl C atoms and the O atoms of the two water molecules were found in the first E map. The four remaining non-H atoms were found in subsequent difference maps. Although most of the H atoms were found in the difference maps, the H atoms attached to the C atoms were placed in idealized positions prior to refinement. Least-squares refinement was performed using 1344 reflections with $|F_o| > 3\sigma(F)$ (R_{merge} = 0.0094). Coordinates for all atoms except the H atoms were refined (on F) by a blocked cascade program in the *SHELXTL* system (Sheldrick, 1985). Anisotropic thermal parameters for the C, N, O and Cl atoms and isotropic thermal parameters for the H atoms attached to N(1) and O(12) were refined for a total of 263 parameters. The C(3)—C(10), C(10)—C(11) and C(3)···C(11) distances were restrained to 1.52, 1.33 and 2.46 Å, respectively. Final R = 6.56% and wR = 6.53%, $w = 1/[\sigma^2(|F|) + 0.0005(F_o)^2]$ for the 8*S*,9*S* configuration. Final R value for the other enantiomorph possessing the 8*R*,9*R* configuration was 7.28%. The absolute configuration that has been established is shown in Figs. 1 and 5. Final difference electron density $|\rho|_{max} = 0.47$ and $|\rho|_{min} = -0.22$ e Å^{-3}. $(\Delta/\sigma)_{max} = 0.11$. $S = 1.88$. Atomic scattering factors were those incorporated in *SHELXTL*.*

Graphics were produced using *SLIDEWRITE-Plus* (Advanced Graphics Software, 1990), *SYBYL* (Tripos Associates, 1991), and the *SHELXTL* program package (Siemens Analytical X-ray Instruments, Inc., 1986).

* 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 55248 (14 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England. [CIF reference: CR0388]

Table 1. *Fractional atomic coordinates* (× 10^4) *and equivalent isotropic thermal parameters* (Å^2 × 10^3) *with e.s.d.'s in parentheses*

$U_{eq} = \frac{1}{3}\sum_i\sum_j U_{ij} a_i^* a_j^* \mathbf{a}_i.\mathbf{a}_j$.

	x	y	z	U_{eq}
N(1)	13428 (6)	3765 (4)	11323 (2)	50 (2)
C(2)	14645 (9)	3174 (6)	11723 (3)	66 (3)
C(3)	16031 (9)	4016 (7)	11908 (1)	77 (3)
C(4)	15759 (10)	5146 (7)	11545 (4)	68 (3)
C(5)	15699 (11)	4870 (8)	10880 (4)	78 (3)
C(6)	14252 (9)	4084 (6)	10741 (3)	60 (3)
C(7)	14119 (8)	5686 (6)	11727 (3)	55 (2)
C(8)	12732 (8)	4798 (5)	11643 (3)	44 (2)
C(9)	11196 (8)	5254 (5)	11320 (3)	42 (2)
C(10)	15867 (14)	4101 (11)	12586 (4)	150 (7)
C(11)	16871 (18)	4591 (10)	12931 (5)	198 (9)
O(12)	10033 (5)	4328 (4)	11262 (2)	55 (2)
N(13)	9014 (8)	8224 (5)	12220 (3)	66 (2)
C(14)	9784 (11)	7390 (8)	12504 (3)	70 (3)
C(15)	10505 (9)	6416 (6)	12249 (3)	55 (2)
C(16)	10397 (8)	6257 (5)	11638 (3)	44 (2)
C(17)	9486 (7)	7106 (5)	11305 (3)	39 (2)
C(18)	9146 (8)	7015 (5)	10687 (3)	45 (2)
C(19)	8355 (9)	7880 (6)	10399 (3)	52 (2)
C(20)	7828 (9)	8892 (7)	10697 (3)	66 (3)
C(21)	8089 (9)	8979 (6)	11298 (3)	65 (3)
C(22)	8880 (9)	8097 (6)	11618 (3)	53 (2)
O(23)	7944 (7)	7874 (4)	9795 (2)	67 (2)
C(24)	8181 (11)	6813 (7)	9468 (3)	71 (3)
Cl	9748 (3)	3956 (2)	9882 (1)	66 (1)
W(1)*	11664 (10)	1743 (6)	10999 (3)	91 (3)
W(2)*	8156 (8)	1990 (6)	10728 (3)	110 (2)
H(1)	12701 (70)	3331 (47)	11293 (23)	52 (17)†
H(12)	10042 (77)	4162 (48)	10941 (24)	66 (19)†

* *W*(1) and *W*(2) represent the O atoms of water molecules.
† These atoms were refined isotropically. The values represent U_{iso}.

Discussion. Table 1 lists the coordinates and U_{eq} values for the non-H atoms and the two H atoms of 9-epiquinine involved in hydrogen bonding. Table 2 lists bond lengths, bond angles and selected torsion angles. The bond length of the H atoms attached to the C atoms was kept fixed at 0.96 Å throughout the refinement procedure.

The conformation and numbering scheme of 9-epiquinine is displayed in Fig. 2. The bicyclo rings of the quinuclidine moiety assume a boat conformation typical of the other cinchona alkaloids. The methylene groups of the quinuclidine ring system nearly eclipse each other as illustrated by the torsion angles C(3)—C(4)···N(1)$^+$—C(2) = −4.0 (7), C(5)—C(4)···N(1)$^+$—C(6) = −2.6 (7) and C(7)—C(4)···N(1)$^+$—C(8) = −5.2 (7)°. The substituents at C(8) and C(3) are *exo* and *endo* with respect to the boat defined by N(1)—C(2)—C(3)—C(4)—C(7)—C(8). The vinyl substituent on C(3) points away from the methoxy group. Atom N(1)$^+$ is *anti* to the quinoline ring with a C(16)—C(9)—C(8)—N(1)$^+$ torsion angle of 177.3 (5)°. As observed in the solution NMR spectrum of 9-epiquinine (Dijkstra, Kellogg, Wynberg, Svendsen, Marko & Sharpless, 1989), H(8) and H(9) are *anti* to each other with an H(8)—C(8)—C(9)—H(9) torsion angle of 174.8 (1)°, and the H(9) atom points toward the methoxy group. The methoxy group is approximately 10° off coplanar with the quinoline ring and points toward the

Table 2. *Bond lengths* (Å), *bond angles* (°) *and selected torsion angles* (°) *with e.s.d.'s in parentheses*

N(1)—C(2)	1.491 (9)	N(1)—C(6)	1.504 (8)
N(1)—C(8)	1.499 (8)	C(2)—C(3)	1.536 (10)
C(3)—C(4)	1.550 (11)	C(3)—C(10)	1.522 (9)
C(4)—C(5)	1.518 (11)	C(4)—C(7)	1.517 (10)
C(5)—C(6)	1.509 (11)	C(7)—C(8)	1.528 (9)
C(8)—C(9)	1.526 (9)	C(9)—O(12)	1.427 (7)
C(9)—C(16)	1.502 (9)	C(10)—C(11)	1.252 (16)
N(13)—C(14)	1.309 (10)	N(13)—C(22)	1.355 (9)
C(14)—C(15)	1.386 (11)	C(15)—C(16)	1.379 (8)
C(16)—C(17)	1.433 (8)	C(17)—C(18)	1.409 (8)
C(17)—C(22)	1.426 (9)	C(18)—C(19)	1.347 (9)
C(19)—C(20)	1.409 (10)	C(19)—O(23)	1.389 (8)
C(20)—C(21)	1.361 (10)	C(21)—C(22)	1.397 (10)
O(23)—C(24)	1.437 (9)		

C(2)—N(1)—C(6)	109.6 (5)	C(2)—N(1)—C(8)	108.9 (5)
C(6)—N(1)—C(8)	112.4 (5)	N(1)—C(2)—C(3)	110.5 (5)
C(2)—C(3)—C(4)	106.8 (5)	C(2)—C(3)—C(10)	104.1 (6)
C(4)—C(3)—C(10)	116.9 (7)	C(3)—C(4)—C(5)	109.8 (5)
C(3)—C(4)—C(7)	109.2 (6)	C(5)—C(4)—C(7)	108.7 (6)
C(4)—C(5)—C(6)	110.6 (6)	N(1)—C(6)—C(5)	108.1 (5)
C(4)—C(7)—C(8)	109.2 (6)	N(1)—C(8)—C(7)	108.5 (5)
N(1)—C(8)—C(9)	110.6 (5)	C(7)—C(8)—C(9)	114.9 (5)
C(8)—C(9)—O(12)	108.6 (5)	C(8)—C(9)—C(16)	112.9 (5)
O(12)—C(9)—C(16)	109.8 (5)	C(3)—C(10)—C(11)	125.8 (10)
C(14)—N(13)—C(22)	116.0 (6)	N(13)—C(14)—C(15)	126.6 (7)
C(14)—C(15)—C(16)	119.1 (6)	C(9)—C(16)—C(15)	122.9 (6)
C(9)—C(16)—C(17)	120.1 (5)	C(15)—C(16)—C(17)	117.0 (5)
C(16)—C(17)—C(18)	123.8 (5)	C(16)—C(17)—C(22)	118.0 (5)
C(18)—C(17)—C(22)	118.2 (5)	C(17)—C(18)—C(19)	120.2 (6)
C(18)—C(19)—C(20)	122.1 (6)	C(18)—C(19)—O(23)	124.9 (6)
C(20)—C(19)—O(23)	113.0 (6)	C(19)—C(20)—C(21)	118.6 (7)
C(20)—C(21)—C(22)	121.4 (7)	N(13)—C(22)—C(17)	123.0 (6)
N(13)—C(22)—C(21)	117.7 (6)	C(17)—C(22)—C(21)	119.3 (6)
C(19)—O(23)—C(24)	117.7 (5)		

C(6)—N(1)—C(2)—C(3)	65.6 (6)	C(8)—N(1)—C(2)—C(3)	−57.9 (6)
C(2)—N(1)—C(6)—C(5)	−58.9 (7)	C(8)—N(1)—C(6)—C(5)	62.5 (7)
C(2)—N(1)—C(8)—C(7)	67.0 (6)	C(2)—N(1)—C(8)—C(9)	−166.1 (5)
C(6)—N(1)—C(8)—C(7)	−54.9 (6)	C(6)—N(1)—C(8)—C(9)	72.0 (6)
N(1)—C(2)—C(3)—C(4)	−6.5 (7)	C(2)—C(3)—C(4)—C(5)	−55.1 (7)
C(2)—C(3)—C(4)—C(7)	64.0 (7)	C(3)—C(4)—C(5)—C(6)	62.4 (8)
C(7)—C(4)—C(5)—C(6)	−56.9 (8)	C(3)—C(4)—C(7)—C(8)	−55.5 (7)
C(4)—C(5)—C(6)—N(1)	−4.3 (8)	C(4)—C(7)—C(8)—N(1)	−8.5 (7)
C(4)—C(7)—C(8)—C(9)	−132.9 (6)	N(1)—C(8)—C(9)—C(16)	177.3 (5)
C(5)—C(4)—C(7)—C(8)	64.2 (8)	N(1)—C(8)—C(9)—O(12)	55.3 (6)
C(7)—C(8)—C(9)—C(16)	−59.4 (7)	C(7)—C(8)—C(9)—O(12)	178.6 (5)
C(8)—C(9)—C(16)—C(15)	−27.9 (8)	C(8)—C(9)—C(16)—C(17)	151.6 (6)
O(12)—C(9)—C(16)—C(15)	93.5 (7)	O(12)—C(9)—C(16)—C(17)	−87.1 (7)
C(22)—N(13)—C(14)—C(15)	1.9 (12)	C(14)—N(13)—C(22)—C(17)	1.8 (10)
C(14)—N(13)—C(22)—C(21)	−179.0 (7)	N(13)—C(14)—C(15)—C(16)	−1.8 (13)
C(14)—C(15)—C(16)—C(9)	177.6 (7)	C(14)—C(15)—C(16)—C(17)	−1.9 (10)
C(9)—C(16)—C(17)—C(18)	6.0 (9)	C(9)—C(16)—C(17)—C(22)	−174.4 (6)
C(15)—C(16)—C(17)—C(18)	−174.5 (6)	C(15)—C(16)—C(17)—C(22)	5.1 (9)
C(16)—C(17)—C(18)—C(19)	−176.6 (6)	C(22)—C(17)—C(18)—C(19)	3.8 (9)
C(16)—C(17)—C(22)—N(13)	−5.3 (10)	C(16)—C(17)—C(22)—C(21)	175.5 (6)
C(18)—C(17)—C(22)—N(13)	174.3 (6)	C(18)—C(17)—C(22)—C(21)	−4.9 (9)
C(17)—C(18)—C(19)—C(20)	−0.5 (10)	C(17)—C(18)—C(19)—O(23)	−179.3 (6)
C(18)—C(19)—C(20)—C(21)	−1.9 (11)	O(23)—C(19)—C(20)—C(21)	177.0 (6)
C(18)—C(19)—O(23)—C(24)	8.6 (10)	C(19)—C(20)—C(21)—C(22)	0.8 (11)
C(20)—C(19)—O(23)—C(24)	−170.3 (6)	C(20)—C(21)—C(22)—N(13)	−176.6 (7)
C(20)—C(21)—C(22)—C(17)	2.6 (11)		

quinuclidine ring system. The $N(1)^+\cdots O(12)$ interatomic distance of 2.816 (8) Å is comparable to the $N^+\cdots O$ distance of 2.791 (6) Å in mefloquine hydrochloride (Karle & Karle, 1991*a*) and slightly longer than the 2.730 (8) Å separation in mefloquine methylsulfonate monohydrate (Karle & Karle, 1991*b*), but shorter than the N···O distance of 3.219 (4) Å in quinine monohydrate toluene solvate (Pniewska & Suszko-Purzycka, 1989), of 3.058 (4) Å in 10-hydroxy-10-methyl-10,11-dihydroquinine (Suszko-Purzycka, Lipińska, Piotrowska & Oleksyn, 1985), and of 3.047 (4) Å in quinidine sulfate (Karle & Karle, 1981).

The vinyl group was not stationary throughout the crystal as indicated by the large thermal parameters listed in Table 1 for atoms C(10) and C(11), and illustrated in Fig. 3. In the difference map based on the parameters for all of the refined atoms in the structure except for C(10) and C(11), the electron density for C(11) was diffuse showing no discrete maximum. Although the *R* factor decreased to 5.7% when the least-squares refinement was run without restraints, the large motion of the vinyl group caused the refined C(10)—C(11) bond length to appear to be too short at 0.979 (16) Å, and the C(3)—C(10)—C(11) angle to be somewhat distorted at 140.8 (13)°. Accordingly, restraints were placed on the C(3)—C(10), C(10)—C(11) and C(3)···C(11) distances in the least-squares refinement which resulted in a C(10)—C(11) bond length equal to 1.252 (16) Å and a C(3)—C(10)—C(11) angle equal to 125.8 (10)°.

Both the hydroxyl group and the $N(1)^+$—H(1) group of 9-epiquinine form intermolecular hydrogen

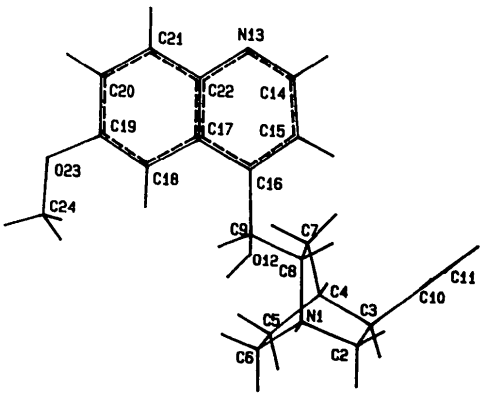

Fig. 2. Conformation and numbering scheme of 9-epiquinine as a tertiary amine salt.

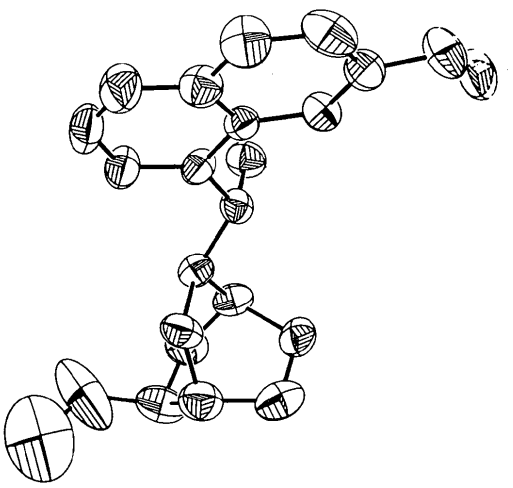

Fig. 3. View of 9-epiquinine down the *b* axis. The thermal ellipsoids are drawn at 50% probability. Only the non-H atoms are shown.

Table 3. *Hydrogen-bond geometry* (Å, °)

E.s.d.'s for the donor–acceptor (*D*···*A*) distance are near 0.008 Å, for the hydrogen–donor (*D*—H) and hydrogen–acceptor (H···*A*) distances are near 0.06 Å, and for the acceptor–hydrogen–donor (*D*—H···*A*) angle are near 4.0°. The H atoms of the water molecules were not located in the difference maps accurately enough to report.

D	H	*A*	*D*···*A*	H···*A*	*D*—H	*D*—H···*A*	Symmetry equivalent of *D*
O(12)	H(12)	Cl	3.117	2.39	0.74	168.9	*x*, *y*, *z*
W(1)	–	Cl	3.270	–	–	–	$-0.5+x$, $0.5-y$, $2-z$
W(2)	–	Cl	3.217	–	–	–	*x*, *y*, *z*
W(2)	–	Cl	3.253	–	–	–	$0.5+x$, $0.5-y$, $2-z$
N(1)	H(1)	*W*(1)	2.826	2.12	0.77	152.3	*x*, *y*, *z*
W(1)	–	*W*(2)	2.905	–	–	–	*x*, *y*, *z*

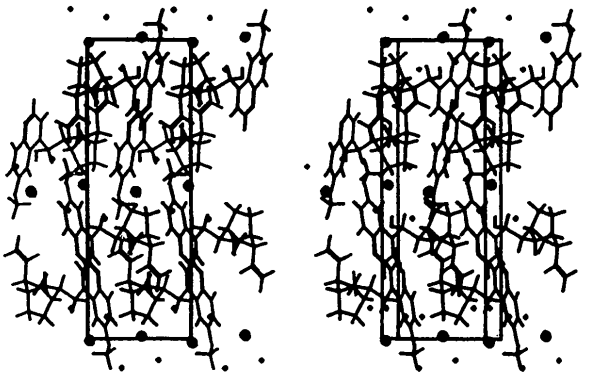

Fig. 4. Packing diagram of 9-epiquinine hydrochloride dihydrate viewed down the *b* axis. The *c* axis is vertical and the *a* axis is horizontal. The large dots represent the location of the Cl ions. The small dots designate the O atoms of the water molecules which form hydrophilic channels parallel to the *a* axis.

bonds. The hydroxyl group of 9-epiquinine forms a hydrogen bond to the Cl ion, and the quinuclidine N atom $N(1)^+$ is hydrogen bonded to *W*(1), one of the two water molecules (Table 3). The Cl ion forms four hydrogen bonds, three with water molecules and one with the hydroxyl group of 9-epiquinine. The water molecules form a hydrophilic channel parallel to the *a* axis as illustrated in the packing diagram of 9-epiquinine hydrochloride dihydrate (Fig. 4).

Since the amine and hydroxyl groups of 9-epiquinine hydrochloride dihydrate preferentially form intermolecular hydrogen bonds and are apparently available for hydrogen bonding to critical cellular constituents, the inactivity of 9-epiquinine is not explained by amine and hydroxyl groups unavailable for intermolecular hydrogen bonding. A shorter $N^+\cdots O$ intramolecular distance than that found in quinine or quinidine also does not explain the inactivity of 9-epiquinine, since the $N^+\cdots O$ distance in 9-epiquinine matches the $N^+\cdots O$ distance in the potent antimalarial mefloquine hydrochloride. However, there is a major structural difference between the inactive 9-epiquinine and the active quinine and quinidine molecules in the relative orientation of the amine and hydroxyl groups. As illustrated in Fig. 5, the position of the C(9)—O(12) bond relative to the position of the $N(1)^+$—H(1) bond differs in 9-epiquinine *versus* quinine and quinidine. This difference is exemplified by the O(12)—C(9)···$N(1)^+$—H(1) torsion angle equal to -0.2 (3.8)° in 9-epiquinine, -117.7° in quinine, and 97.0° in quinidine. The difference in torsion angles causes the O(12)—H(12) and $N(1)^+$—H(1) bonds to point in different relative directions as well as places H(1) of the tertiary amine salt over 1 Å closer to O(12) of the hydroxyl group in 9-epiquinine than in quinine or in quinidine. Therefore, the inactivity of 9-epiquinine may be a result of an unfavorable positioning of the amine and hydroxyl groups such that hydrogen bonds to cellular constituents critical to antimalarial activity cannot be made with similar geometry.

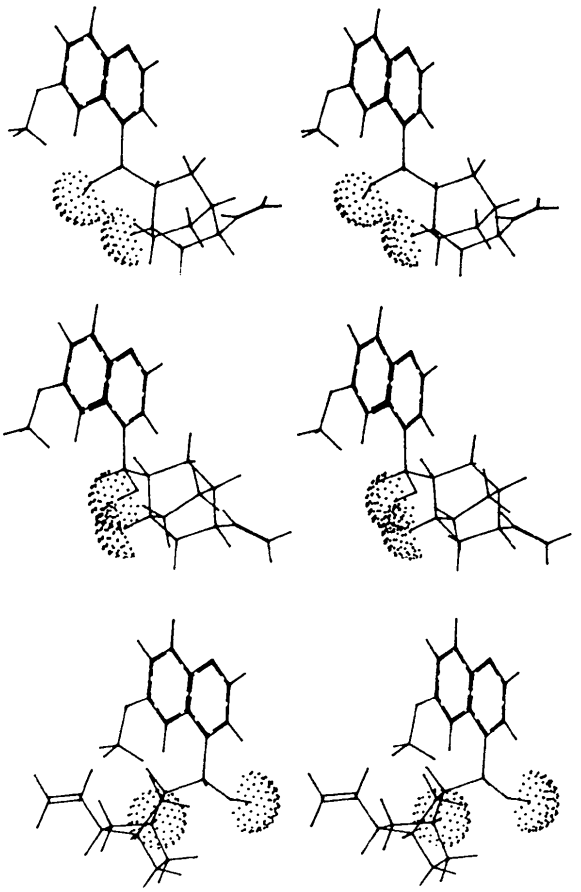

Fig. 5. Stereodiagrams of 9-epiquinine (top), quinidine (middle) (Karle & Karle, 1981) and quinine (bottom) (Pniewska & Suszko-Purzycka, 1989). All of the drawings have been made with the quinoline ring in the identical orientation. The dotted surfaces represent the van der Waals radii of the H atoms attached to O(12) and $N(1)^+$. Although crystallized in free base form, an H atom has been added to the quinuclidine N atom of quinine in an idealized position to form a tertiary amine salt.

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Structure of Pentacyclo[8.5.0.0^{2,7}.0^{4,13}.0^{5,1}]pentadeca-8,14-diene-3,6-dione

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Abstract. $C_{15}H_{14}O_2$, $M_r = 226.27$, monoclinic, $P2_1/n$, $a = 7.7505$ (9), $b = 16.484$ (2), $c = 8.7383$ (9) Å, $\beta = 101.16$ (1)°, $V = 1095.2$ (2) Å^3, $Z = 4$, $D_x = 1.372$ g cm^{-3}, λ(Mo $K\alpha$) = 0.7107 Å, $\mu = 0.84$ cm^{-1}, $F(000) = 480$, $T = 295$ K, $R(F_o) = 0.041$, $wR = 0.049$ for 1205 observed reflections with $|F_o| \geq 5.0(F_o)$. The five-membered ring has an envelope conformation, while the two six-membered rings are in twist form. In the unit cell, the molecules are stabilized purely by van der Waals forces.

Introduction. It is well known that synthesis of higher prismanic frameworks is a formidable task owing to the problems posed by considerably higher steric energy and the large deviation in the tetrahedral C—C—C angle from the normal range. A series of probing experiments on the heptacyclic ketones in quest for [7]-prismane homo- and secologues have been carried out. In this process three novel polyhedranes were synthesized through thermal [2 + 2] cyclo reversion of heptacyclic triones; a decarboxylated rearrangement product was also obtained (Mehta, Harikrishna Reddy & Padma, 1991). The title compound is this rearrangement product, a crystallographic study of which was undertaken to establish its molecular structure.

Experimental. Thin transparent colourless needle-shaped crystals were crystallized from dichloromethane–hexane mixture. A single crystal of size 0.25 × 0.15 × 0.1 mm was used for collection of a three-dimensional intensity-data set on an Enraf–Nonius CAD-4 automated X-ray diffractometer with monochromated Mo $K\alpha$ radiation; $\omega/2\theta$ scan mode with $\omega = (0.6 + 0.35\tan\theta)°$; aperture width = (1.8 +

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