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Structure of the Antimalarial (±)-Mefloquine Hydrochloride

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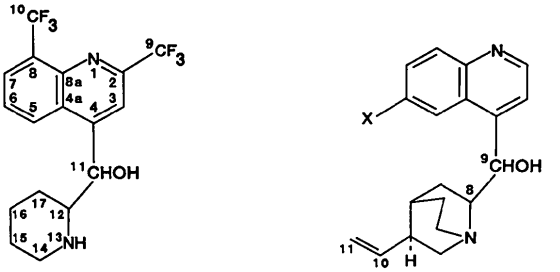
Abstract. (11*R**,12*S**)-(±)-α-2-Piperidinyl-2,8-bis-(trifluoromethyl)-4-quinolinemethanol monohydrochloride, $C_{17}H_{17}F_6N_2O^+.Cl^-.0{\cdot}5CH_3OH$, M_r = 430·8, tetragonal, $P4_2/n$ (origin at center of symmetry), $a = b = 24{\cdot}595$ (4), $c = 6{\cdot}398$ (2) Å, V = 3870·0 Å^3, $Z = 8$, $D_x = 1{\cdot}48$ g cm^{-3}, Cu $K\alpha$, λ = 1·54178 Å, $\mu = 24{\cdot}28$ cm^{-1}, $F(000) = 1768$, room temperature, final $R = 7{\cdot}5\%$ for 2067 reflections with $|F_o > 3\sigma(F)$. Mefloquine hydrochloride crystallized as a secondary amine salt with channels of disordered methanol solvent. The trifluoromethyl group on the C adjacent to the quinoline N atom exhibited rotational disorder. Each chloride ion accepts three hydrogen bonds, one each from the hydroxyl group and the two H atoms of the amine group of mefloquine from three separate molecules. The angle between the average plane of the quinoline ring and the average plane of the piperidine ring is 110·5°.

Introduction. (±)-Mefloquine hydrochloride was developed by the Walter Reed Army Institute of Research and Roche Laboratories (Nutley, NJ) as an alternative treatment for multi-drug-resistant malaria. (±)-Mefloquine hydrochloride was approved for treating malaria in 1989 by the Food and Drug Administration and is marketed under the trade name Lariam. Not only is malaria a disease of worldwide epidemic proportions with estimated yearly cases in the 100 millions and an estimated yearly death rate in the millions, chloroquine-resistant malaria, first confirmed in South America and Southeast Asia in the 1960's, now resides in malaria endemic areas around the globe (Wyler, 1983; Payne, 1987).

Mefloquine is a quinoline-containing amino alcohol antimalarial whose structure is derived from the cinchona alkaloids (Fig. 1). Mefloquine has a different substitution pattern on the quinoline ring than the cinchona alkaloids and a piperidine ring substituting for the bulkier bicyclo quinuclidine ring of the cinchona alkaloids. All four of the cinchona alkaloids pictured in Fig. 1 have demonstrated clinical antimalarial activity against human-infecting parasites (Earle *et al.*, 1948; Taggart *et al.*, 1948).

Both mefloquine enantiomers have been individually tested for antimalarial activity against *Plasmodium berghei* in mice and demonstrated comparable antimalarial activity to mefloquine racemate (Sweeney, 1981). As is common with natural products, the cinchona alkaloids occur only in the enantiomeric form listed in Fig. 1. Although quinine and cinchonidine (the 8*S*,9*R* alkaloids) are diastereomers of quinidine and cinchonine (the 8*R*,9*S* alkaloids), due to other asymmetric centers in



Mefloquine: 11*R*,12*S* (11*S*,12*R*)

Quinine: *X* = OMe, 8*S*,9*R*
Quinidine: *X* = OMe, 8*R*,9*S*
Cinchonine: *X* = H, 8*R*,9*S*
Cinchonidine: *X* = H, 8*S*,9*R*

Fig. 1. Chemical structures of mefloquine and the active cinchona alkaloids drawn as the free base. The numbering scheme used for mefloquine is illustrated. The structures were drawn using *SLIDEWRITEPlus* from Advanced Graphics Software, Inc. (Sunnyvale, CA).

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the bicyclo quinuclidine ring system, the amine and hydroxyl portions of the molecules essentially mirror each other when the quinoline rings are superimposed (Karle & Karle, 1989). The absolute configuration of quinidine and cinchonine was confirmed by X-ray analysis (Carter, McPhail & Sim, 1967; Oleksyn, Stadnicka & Hodorowicz, 1978).

The crystal structure of mefloquine hydrochloride was found to be similar to the crystal structures of the active cinchona alkaloids in terms of orientation of the piperidine ring with respect to both the quinoline ring and the hydroxyl group and the aliphatic N to hydroxyl O distance.

Experimental. (±)-Mefloquine free base was crystallized from HCl-saturated methanol to yield crystals of mefloquine hydrochloride. Diffraction data were collected from a colorless cloudy prism, 0·25 × 0·25 × 1·0 mm, in the θ–2θ mode to a maximum 2θ value of 112° on an *R*3*m*/micro Nicolet four-circle diffractometer (Siemens Corporation, Madison, WI) with a graphite monochromator. Range of indices: h 0→27, k 0→27 and l 0→7. The total number of reflections measured was 3054 and the number of independent reflections was 2801. The standard reflections $\bar{1}0,0,0$, 0,10,0 and 002 were monitored after every 60 intensity measurements. The standards varied by up to 2·5%. The lattice parameters were based on 25 centered reflections with 2θ values between 32 and 45°. No correction for absorption or extinction was applied. The structure was solved routinely by direct phase determination (Karle & Karle, 1966). All of the non-H atoms except for the methanol molecules and the positions of the disordered F atoms were found in the first *E* map. All of the H atoms, the disordered F atoms, and the C*m* and O*m* atoms of the disordered methanol solvent were found in subsequent difference maps. All of the H atoms except H(O) were placed in idealized positions. Least-squares refinement was performed using 2067 reflections with $|F_o| > 3\sigma(F)$ ($R_{merge} = 0{\cdot}0069$). Coordinates for all atoms except the H atoms on the N and C atoms were refined (on *F*) by a blocked-cascade program in the *SHELXTL* system (Sheldrick, 1980). Anisotropic thermal parameters for the C, N, O and F atoms of mefloquine and the chloride ion and isotropic thermal parameters for H(O), the disordered F atoms located in three different positions weighted 0·58, 0·25 and 0·18, and the disordered solvent molecules weighted 0·5 were refined for a total of 265 parameters. The weights for the F atoms of the disordered trifluoromethyl group were chosen such that the thermal factors for the three positions were comparable. No other peaks of electron density appeared in the region of the disordered trifluoromethyl group. The weights for the disordered solvent molecules were arbitrarily assigned. Final $R = 7{\cdot}5\%$ and $wR = 10{\cdot}4\%$, $w = 1/[\sigma^2(|F|) + 0{\cdot}001(F_o)^2]$, $S = 2{\cdot}1$, $(\Delta/\sigma)_{max} = 0{\cdot}43$. Final difference electron density $|\rho|_{max} = 0{\cdot}47$ and $|\rho|_{min} = -0{\cdot}29$ e Å^{-3}. Atomic scattering factors were those incorporated in *SHELXTL*.*

Table 1. *Fractional coordinates* ($\times 10^4$) *and thermal parameters* U_{eq} (Å$^2 \times 10^3$) *with e.s.d.'s in parentheses for* (11*R*,12*S*)*-mefloquine hydrochloride*

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

	x	y	z	U_{eq}
O	3867 (1)	6514 (1)	1509 (5)	73 (1)
N(1)	5895 (2)	6248 (2)	1661 (7)	70 (2)
C(2)	5488 (2)	6064 (2)	559 (7)	67 (2)
C(3)	4941 (2)	6181 (2)	996 (7)	65 (2)
C(4)	4815 (2)	6508 (2)	2653 (7)	60 (2)
C(4a)	5248 (2)	6727 (2)	3862 (7)	61 (2)
C(5)	5167 (2)	7077 (2)	5595 (8)	77 (2)
C(6)	5602 (3)	7265 (2)	6670 (11)	97 (3)
C(7)	6135 (2)	7117 (2)	6129 (10)	99 (3)
C(8)	6225 (2)	6792 (2)	4472 (9)	78 (2)
C(8a)	5785 (2)	6584 (2)	3282 (8)	65 (2)
C(9)	5623 (3)	5679 (3)	−1188 (10)	89 (2)
C(10)	6801 (2)	6631 (3)	3918 (13)	102 (3)
C(11)	4216 (2)	6600 (2)	3232 (7)	59 (2)
C(12)	4035 (2)	6218 (2)	4943 (7)	61 (2)
N(13)	3472 (2)	6365 (2)	5560 (6)	68 (2)
C(14)	3247 (2)	6026 (3)	7295 (9)	87 (2)
C(15)	3267 (2)	5430 (2)	6741 (10)	99 (3)
C(16)	3834 (3)	5260 (2)	6122 (10)	101 (3)
C(17)	4056 (2)	5623 (2)	4378 (9)	80 (2)
F(1)*	6121 (4)	5806 (4)	−2031 (15)	117 (3)†
F(2)*	5619 (2)	5175 (2)	−578 (9)	96 (2)†
F(3)*	5258 (4)	5709 (4)	−2787 (12)	94 (2)†
F(1′)*	5330 (5)	5157 (4)	−844 (19)	68 (3)†
F(2′)*	6150 (5)	5509 (7)	−1228 (23)	80 (4)†
F(3′)*	5491 (8)	5843 (5)	−2919 (20)	66 (4)†
F(1″)*	5166 (8)	5455 (10)	−2263 (37)	95 (7)†
F(2″)*	5927 (8)	5253 (7)	−591 (22)	52 (4)†
F(3″)*	5877 (11)	5893 (7)	−2701 (31)	79 (5)†
F(4)	7163 (1)	6872 (2)	5161 (8)	142 (2)
F(5)	6935 (1)	6759 (2)	1970 (7)	117 (2)
F(6)	6886 (1)	6100 (1)	4129 (7)	124 (2)
Cl	2408 (1)	6169 (1)	2928 (3)	99 (1)
O*m*‡	2896 (8)	7437 (8)	3132 (47)	272 (9)†
C*m*‡	2485 (28)	7326 (33)	5530 (106)	440 (30)†
H(O)	3925 (21)	6725 (21)	613 (87)	114 (19)†
H(13*A*)	3471	6739	5998	77§
H(13*B*)	3241	6324	4361	77§

* These F atoms were disordered and were weighted 58, 25 and 18%, respectively.

† These atoms were refined isotropically. The values represent U_{iso}.

‡ The C*m* and O*m* atoms represent methanol solvent molecules disordered across a twofold axis and were weighted 50%.

§ These atoms were placed in idealized positions.

Discussion. Table 1 lists the coordinates and U_{eq} values for the non-H atoms and coordinates for the H atom of the hydroxyl group. Table 2 lists selected bond lengths, bond angles and torsion angles for mefloquine. The bond length of the H atoms attached to the C and N atoms was kept fixed at 0·96 Å throughout the refinement procedure.

Mefloquine (Figs. 1 and 2) crystallized as a secondary amine hydrochloride salt. Parallel to the *c*

* 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 54256 (21 pp.). Copies may be obtained through The Technical Editor, International Union of Crystallography, 5 Abbey Square, Chester CH1 2HU, England.

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

O—C(11)	1·414 (5)	N(1)—C(2)	1·306 (6)
N(1)—C(8a)	1·352 (6)	C(2)—C(3)	1·405 (7)
C(2)—C(9)	1·502 (8)	C(3)—C(4)	1·365 (6)
C(4)—C(4a)	1·422 (6)	C(4)—C(11)	1·536 (6)
C(4a)—C(5)	1·418 (7)	C(4a)—C(8a)	1·417 (7)
C(5)—C(6)	1·353 (8)	C(6)—C(7)	1·405 (8)
C(7)—C(8)	1·347 (8)	C(8)—C(8a)	1·418 (7)
C(8)—C(10)	1·514 (8)	C(11)—C(12)	1·510 (6)
C(12)—N(13)	1·485 (6)	C(12)—C(17)	1·508 (7)
N(13)—C(14)	1·495 (7)	C(14)—C(15)	1·510 (8)
C(15)—C(16)	1·507 (9)	C(16)—C(17)	1·531 (8)

C(2)—N(1)—C(8a)	118·2 (4)	N(1)—C(2)—C(3)	123·8 (4)
N(1)—C(2)—C(9)	116·8 (5)	C(3)—C(2)—C(9)	119·3 (5)
C(2)—C(3)—C(4)	119·5 (4)	C(3)—C(4)—C(4a)	118·4 (4)
C(3)—C(4)—C(11)	119·4 (4)	C(4a)—C(4)—C(11)	122·0 (4)
C(4)—C(4a)—C(5)	123·5 (4)	C(4)—C(4a)—C(8a)	117·5 (4)
C(5)—C(4a)—C(8a)	119·0 (4)	C(4a)—C(5)—C(6)	119·6 (5)
C(5)—C(6)—C(7)	121·7 (6)	C(6)—C(7)—C(8)	120·0 (5)
C(7)—C(8)—C(8a)	120·8 (5)	C(7)—C(8)—C(10)	119·6 (5)
C(8a)—C(8)—C(10)	119·6 (5)	N(1)—C(8a)—C(4a)	122·6 (4)
N(1)—C(8a)—C(8)	118·6 (4)	C(4a)—C(8a)—C(8)	118·8 (4)
O—C(11)—C(4)	111·9 (3)	O—C(11)—C(12)	107·0 (3)
C(4)—C(11)—C(12)	111·4 (4)	C(11)—C(12)—N(13)	108·4 (4)
C(11)—C(12)—C(17)	114·9 (4)	N(13)—C(12)—C(17)	109·4 (4)
C(12)—N(13)—C(14)	114·0 (4)	N(13)—C(14)—C(15)	110·9 (5)
C(14)—C(15)—C(16)	111·2 (5)	C(15)—C(16)—C(17)	111·1 (5)
C(12)—C(17)—C(16)	112·3 (5)		

C(2)—C(3)—C(4)—C(11)	−175·4 (4)	C(11)—C(4)—C(4a)—C(5)	−4·6 (7)
C(11)—C(4)—C(4a)—C(8a)	175·5 (4)	C(3)—C(4)—C(11)—O	−23·7 (6)
C(3)—C(4)—C(11)—C(12)	95·9 (5)	C(4a)—C(4)—C(11)—O	159·9 (4)
C(4a)—C(4)—C(11)—C(12)	−80·4 (5)	O—C(11)—C(12)—N(13)	−62·8 (4)
C(4)—C(11)—C(12)—N(13)	174·7 (3)	O—C(11)—C(12)—C(17)	59·9 (5)
C(11)—C(12)—N(13)—C(14)	−178·4 (4)	C(4)—C(11)—C(12)—C(17)	−62·7 (5)
C(11)—C(12)—C(17)—C(16)	−176·3 (4)	C(17)—C(12)—N(13)—C(14)	55·7 (5)
C(12)—N(13)—C(14)—C(15)	−56·2 (6)	N(13)—C(12)—C(17)—C(16)	−54·2 (6)
C(15)—C(16)—C(17)—C(12)	54·6 (6)	C(14)—C(15)—C(16)—C(17)	−53·8 (6)

axis the crystal also contains channels containing peaks of electron density which were ascribed to disordered methanol solvent molecules. Alternatively, these peaks of electron density could have been modeled as water molecules. The choice was made to consider them as peaks of disordered solvent since none of the peaks appear at appropriate distances for hydrogen bonding to the chloride ions as would be expected by hydrated hydrochloride salts. The trifluoromethyl group containing C(9) is disordered and was refined in three differently rotated positions defined by the three torsion angles C(3)—C(2)—C(9)—F(1), C(3)—C(2)—C(9)—F(1′) and C(3)—C(2)—C(9)—F(1″) of 151·1 (6), −54·8 (8) and −0·7 (1·3)°. These rotamers were represented 58, 25 and 18% of the time, repectively. The N(13)···O interatomic distance of 2·791 (6) Å is slightly smaller than the aliphatic N···O interatomic distance observed in the active cinchona alkaloids of 2·84 to 3·22 Å (Allen, Kennard & Taylor, 1983; Carter, McPhail & Sim, 1967; Doherty, Benson, Maienthal & Stewart, 1978; Karle & Karle, 1981; Kashino & Haiso, 1983; Oleksyn, Lebioda & Ciechanowicz-Rutkowska, 1979; Oleksyn, 1978, 1982; Oleksyn, Stadnicka & Hodorowicz, 1978; Pniewska & Suszko-Purzycka, 1989). The piperidine ring assumes a chair conformation. The piperdine ring is almost perpendicular to the plane of the quinoline ring as demonstrated by the 110·5° angle between the average planes of the quinoline and piperidine rings and by the C(4)—C(11)—C(12)—N(13) torsion angle of 174·7 (3)° for (11*R*,12*S*)-mefloquine. The comparable torsion angle in the active cinchona alkaloids varies from 147·4 to 158·1° for quinine and cinchonidine (the 8*S*,9*R* alkaloids) and from −160·3 to 171·4° for quinidine and cinchonine (the 8*R*,9*S* alkaloids).

Mefloquine is *erythro* about C(11) and C(12) as are the active cinchona alkaloids quinine, quinidine, cinchonine and cinchonidine. The O—C(11)—C(12)—N(13) torsion angle for the (11*R*,12*S*)-mefloquine and (11*S*,12*R*)-mefloquine is (− or +) 62·8 (4)°, respectively, which is in the same range as the corresponding torsion angles found in the crystalline forms of quinidine and cinchonine of 48·3 to 76·1° and slightly smaller than the −77·8 to −89·5° found in quinine and cinchonidine. When

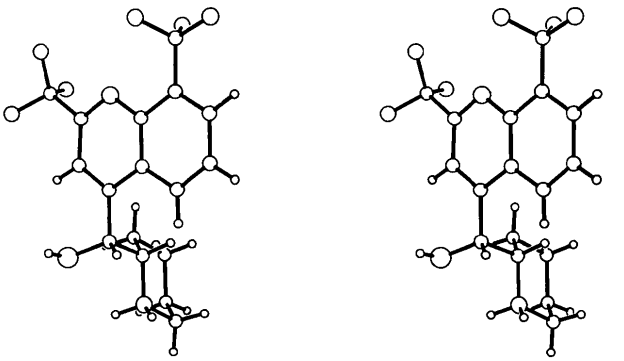

Fig. 2. Stereodiagram of (11*R*,12*S*)-mefloquine. The size of the spheres was arbitrarily chosen to correspond to the atomic weight of the atom. To simplify the diagram, only the F(1), F(2) and F(3) atoms on C(9) are illustrated. The figure was drawn using the *SHELXTL* program package.

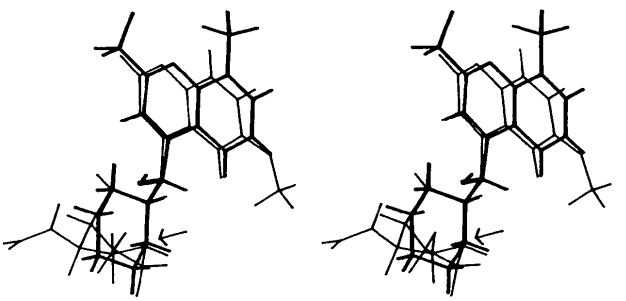

Fig. 3. Stereodiagram of mefloquine (heavy lines) superimposed with the cinchona alkaloid quinidine (light lines). Atoms O(1), C(11), C(12) and N(13) of (11*S*,12*R*)-mefloquine are superimposed with the corresponding atoms of quinidine sulfate (Karle & Karle, 1981). The arrow points to $N(13)^+$ of mefloquine and the N^+ atom of quinidine. To simplify the diagram, only the F(1), F(2) and F(3) atoms on C(9) of mefloquine are illustrated. The figure was drawn using the *SYBYL* program from Tripos Associates (St Louis, MO).

Table 3. *Hydrogen-bond distances and angles*

Donor atom	Hydrogen atom	Acceptor atom	Distance donor–acceptor* (Å)	Distance hydrogen–acceptor* (Å)	Angle acceptor–hydrogen–donor* (°)	Symmetry equivalent of donor
O	H(O)	Cl	3·177	2·41	163·9	$-0{\cdot}5+y, 1-x, 0{\cdot}5+z$
N(13)	H(13*A*)	Cl	3·106	2·24	149·6	$-0{\cdot}5+y, 1-x, -0{\cdot}5+z$
N(13)	H(13*B*)	Cl	3·150	2·28	150·7	x, y, z

* E.s.d.'s for the donor–acceptor and the hydrogen–acceptor distances are near to 0·007 and 0·07 Å, respectively, and for the acceptor–hydrogen–donor angle are near to 0·5°.

quinine is derivatized in the vinyl position to yield 10-hydroxy-10-methyl-10,11-dihydroquinine, the O—C—C—N torsion angle decreased to −71·9 (2)° (Suszko-Purzycka, Lipinska, Piotrowska & Oleksyn, 1985). The superposition of mefloquine hydrochloride with quinidine sulfate (Fig. 3) illustrates the similarity of the conformation of the two antimalarial agents. The four atoms corresponding to O(1), C(11), C(12) and N(13)$^+$ of the two molecules were subjected to a least-squares fit, and the arrow indicates the location of the aliphatic N atoms of both molecules.

Both of the H atoms attached to N(13) and the H atom of the hydroxyl group form hydrogen bonds with the chloride ions (Table 3, Fig. 4). Each chloride ion participates in three hydrogen bonds. Atoms H(13*A*) and H(O) from the same mefloquine molecule hydrogen bond to separate chloride ions displaced by one unit cell in the *c* direction. Since the cinchona alkaloids contain tertiary amine groups, salts of the cinchona alkaloids can form only one hydrogen bond with the amine group. This hydrogen bond corresponds to H(13*A*)···Cl of mefloquine hydrochloride. None of the methanol solvent molecules form hydrogen bonds with either the mefloquine molecules or the chloride ions. The O*m* atom is not properly placed to form a fourth hydrogen bond with the chloride ions in a tetrahedral manner.

The packing diagram illustrates the fourfold symmetry of mefloquine molecules and chloride ions encircling the channel of disordered solvent molecules (Fig. 4). The trifluoromethyl groups line up diagonally to the *a* and *b* axes in both directions forming continuous strings of trifluoromethyl groups and a diamond-like pattern surrounding sets of four mefloquine molecules, four chloride ions and the disordered solvent channel. Atoms F(4), F(5) and F(6) are at least 2·98 Å from F atoms on neighboring trifluoromethyl groups. All of the intermolecular F—F contacts involving the disordered trifluoromethyl group are longer than 3 Å except for the following three possibililites: F(1′)···F(2) of 2·64, F(1′)···F(1″) of 2·78, and F(1′)···F(1′) of 2·10 Å. Due to the small F(1′)···F(1′) distance, it is unlikely that this configuration (of the various configurations possible in the rotational disorder) exists between neighboring molecules. The O*m* and C*m* atoms of the methanol solvent were found to be disordered about a twofold axis and were refined as if in 50% occupancy. However, since the O*m*—C*m* distance is a lengthy 1·857 Å, the atoms were not connected by a bond in the packing diagram, and the methanol molecules most likely contain additional disorder.

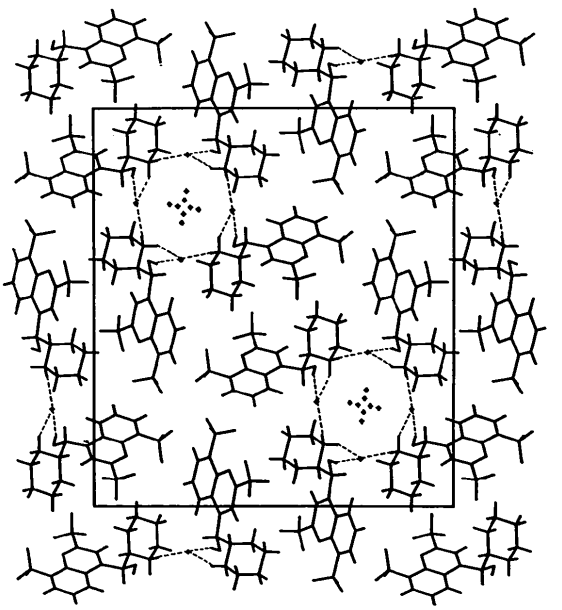

Fig. 4. Packing diagram of mefloquine hydrochloride viewed down the *c* axis. The hydrogen bonds between the mefloquine molecules and the chloride ions are depicted by the dotted lines. To simplify the diagram, only the F(1), F(2) and F(3) atoms on C(9) are illustrated. The small crosses represent the location of the chloride ions and the C*m* and O*m* atoms of the disordered methanol molecules. The bond between C*m* and O*m* was not drawn. The figure was drawn using the *SYBYL* program from Tripos Associates (St Louis, MO).

In summary, the overall conformation of mefloquine is similar to the active cinchona alkaloids such that when the quinoline rings of mefloquine and the cinchona alkaloids are superimposed, the piperidine ring of mefloquine is positioned in the same manner as the quinuclidine ring system of the cinchona alkaloids. Since the hydroxyl groups and the H atoms of the aliphatic amine salts of mefloquine and the cinchona alkaloids are superimposable, both mefloquine and the cinchona alkaloids should be able to form hydrogen bonds in the same direction.

The pattern of hydrogen bonding exhibited by mefloquine hydrochloride demonstrates that mefloquine should be able to hydrogen bond with molecules of biological importance such as transport proteins or cellular 'effectors' of antimalarial action.

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Structure of Fluorescein Dihexanoate*

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Abstract. 3-Oxospiro[isobenzofuran-1(3*H*),9′-[9*H*]-xanthene]-3′,6′-diyl hexanoate, $C_{32}H_{32}O_7$, M_r = 528·28, orthorhombic, *Pbca*, a = 21·864 (3), b = 19·222 (3), c = 13·117 (3) Å, V = 5512·5 Å^3, Z = 8, D_x = 1·274 g cm^{-3}, λ(Mo $K\alpha$) = 0·7107 Å, μ(Mo $K\alpha$) = 0·834 cm^{-1}, T = 298 K, $F(000)$ = 2240, R = 0·06661 for 2086 unique observed reflections. Unlike fluorescein dipropionate, the title compound did not form an inclusion compound with the solvent acetone. The diffraction analysis reveals that both OH groups in fluorescein participated in esterification.

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Introduction. This paper describes a continuation of our investigations on fluorescent materials. The structures of 3,6-dichlorofluoran (Wang, Ren, Wang, He, Wang, Jin & Zhang, 1989) and fluorescein dipropionate (Wang, Wang, Peng, He & Wang, 1990) and the antitumor activity of the former have previously been reported. In this article, we describe the structure of an ester of fluorescein with a larger aliphatic acid, hexanoic acid.

Experimental. The title compound (I) was prepared by refluxing fluorescein (II) with hexanoic acid anhydride (in molar ratio 1:5) in the presence of pyridine and was crystallized from acetone. The colorless crystals of (I) are stable in the atmosphere, m.p. 377–378 K. The infrared spectrum of (I) showed

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