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## Crystal and Molecular Structure of (9R)-10,11-dihydro-6'-methoxy-cinchonan-9-ol-4-chlorobenzoate hydrochloride

The crystal structure of the title compound has been determined by single crystal X-ray diffraction methods.  $C_{27}H_{29}N_3O_3Cl.HCl$  is one of the cinchona alkaloids. It crystallizes in the space group  $P2_12_12_1$  with  $a = 11.745(3)$ ,  $b = 12.353(6)$ ,  $c = 17.253(6)$  Å and  $Z = 4$ . The structure was refined to a final R value of 0.062 for 2155 observed reflections. The C—N distances are unequal in the quinoline ring system. In quinulidine ring, the bonds around N are more tetrahedral. The spatial arrangement and torsion angles show the open conformation of the molecule. The molecular packing is stabilized by hydrogen bonding.

Keywords: crystal structure

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### 1. Introduction

Cinchona is a rubiaceaceous genus of trees, yielding the bark from which quinine and its congeners can be obtained. Cinchona contains a mixture of more than twenty alkaloids which gives promising opportunity for the study of relationship between chemical structure and pharmacological action. Cinchona alkaloids are pharmacologically potent drugs (GOODMAN and GILLMAN, 1985) useful for the treatment of malarial diseases, but their contribution in chemistry is also important (GRETHE and USKOKOVIC, 1983). The most important and interesting application of cinchona alkaloids resides in their ability to induce asymmetry when employed as chiral adjuvants. Several reviews have discussed in detail the cinchona alkaloids and their potential use as chiral catalyst (WYNBERG, 1986). The title compound was investigated to understand the exact conformation of the molecule with HCl in the crystals. Its structure has been compared with similar structures.

### 2. Experimental

A well formed plate shaped crystal of dimension 1.6x1.7x0.5 mm was used for the intensity data collection. Accurate values for the cell parameters were derived by least-squares refinement from 25 well centred reflections on CAD-4 Enraf-Nonius diffractometer  $CuK\alpha$  radiation in the  $2\theta$  range 7–37°. The intensities were measured at room temperature in  $\omega$ -2 $\theta$  scan mode with graphite monochromator. 2625 reflections were measured in the range  $4.4 < \theta < 70.08^\circ$  of which 2155 unique reflections were considered observed with  $I > 2\sigma(I)$ . The intensities of three control reflections recorded during the data collection every one hour, remained constant within  $\pm 3\%$ . The hkl range in which the data were collected was  $0 \leq h \leq$

14,  $0 \leq k \leq 13$  and  $0 \leq l \leq 21$ . The data were corrected for Lorentz and polarisation effect (GABE, LE PAGE, WHITE and LEE, 1987) and absorption correction (NORTH et al., 1968). The crystal data and experimental details are given in Table 1.

Table 1: Crystal data and structure refinement details

Empirical formula	$C_{27}H_{29}ClN_2O_3 \cdot HCl$
$M_r$	501.43
Temperature	293(2) K
Wavelength (Cu $K\alpha$ )	1.5418 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 11.745(3)$ Å $b = 12.353(6)$ Å $c = 17.253(6)$ Å
Volume	$2503.2(2)$ Å <sup>3</sup>
Z	4
Density (calculated)	$1.331$ Mg/m <sup>3</sup>
Absorption coefficient	$2.586$ mm <sup>-1</sup>
Absorption correction:	
Empirical $\psi_{\text{scan}}$ (NORTH et al., 1968); $T_{\text{min}} = 0.61$ ; $T_{\text{max}} = 0.85$	
F(000)	1056
Crystal size	$1.6 \times 1.7 \times 0.5$ mm
Theta maximum for data collection	$70.08^\circ$
Reflections collected	2625
Independent reflections	2155
Goodness-of-fit on $F^2$	1.087
Final R indices [ $I > 2\sigma(I)$ ]	$R(F) = 0.062$ , $wR(F^2) = 0.166$
R indices (all data)	$R(F) = 0.075$ , $wR(F^2) = 0.176$
Absolute structure parameter (FLACK, 1983)	$-0.01(4)$
Largest diff. peak and hole	$0.29$ and $-0.32$ e Å <sup>-3</sup>

Table 2: Atomic co-ordinates ( $\times 10^4$ ) and equivalent isotropic displacement parameters (Å<sup>2</sup>,  $\times 10^3$ ) for non-H atoms with e.s.d.'s

Atom	x	y	z	$U_{\text{eq}}$
C(1)	4210(5)	8214(5)	7275(3)	54(1)
C(2)	4847(5)	7201(5)	7579(3)	54(1)
C(3)	4262(5)	6207(6)	7236(4)	58(2)
C(4)	4272(5)	6246(5)	6349(4)	61(2)
C(5)	3679(4)	7303(5)	6077(3)	51(1)
C(6)	2422(5)	7188(6)	7244(4)	59(2)
C(7)	3025(6)	6154(6)	7520(5)	76(2)
C(8)	6118(5)	7249(6)	7401(4)	67(2)
C(9)	6720(6)	8143(7)	7826(5)	93(3)
C(10)	2788(4)	7158(5)	5438(3)	45(1)
C(11)	1301(4)	5927(5)	5093(3)	49(1)
C(12)	812(4)	4864(5)	5233(3)	47(1)
C(13)	-62(5)	4512(5)	4743(3)	53(1)
C(14)	-578(5)	3528(5)	4867(4)	61(2)
C(15)	-238(6)	2909(6)	5472(4)	67(2)

C(16)	629(7)	3224(7)	5955(5)	90(3)
C(17)	1132(6)	4212(6)	5842(4)	75(2)
C(18)	3395(4)	7134(5)	4660(3)	49(1)
C(19)	3958(5)	6189(5)	4448(4)	62(2)
C(20)	4603(6)	6185(6)	3756(4)	71(2)
C(21)	4151(5)	7924(5)	3488(3)	51(1)
C(22)	4255(6)	8824(6)	2986(4)	67(2)
C(23)	3701(6)	9760(6)	3112(3)	64(2)
C(24)	2980(5)	9848(5)	3762(3)	58(2)
C(25)	2873(5)	9035(5)	4287(3)	54(1)
C(26)	3456(4)	8037(5)	4165(3)	44(1)
C(27)	1601(6)	10972(6)	4404(4)	78(2)
N(1)	3224(4)	7868(4)	6779(3)	48(1)
N(2)	4719(5)	6988(5)	3301(3)	68(2)
O(1)	2183(3)	6162(3)	5582(2)	47(1)
O(2)	996(3)	6574(4)	4608(3)	62(1)
O(3)	2438(4)	10825(4)	3809(3)	70(1)
Cl(1)	-941(2)	1690(2)	5652(2)	99(1)
Cl(2)	7582(1)	5025(1)	8711(1)	66(1)

### 3. Structure analysis

The structure was solved by direct methods program incorporated into the SHELX86 system (SHELDRICK, 1990). The E-map computed for the best solution reveals the positions of all non-H atoms of the molecule along with an extra peak. The extra peak after proper inspection was assigned as chlorine atom. The parameters of these atoms were first refined isotropically and then anisotropically by full matrix least-square method using the program SHELXL93 (SHELDRICK, 1993). The H-atoms positions were positioned geometrically and refined using riding model. The parameters at the end of the final refinement converged to  $R(F) = 0.062$  and  $wR(F^2) = 0.166$  with  $(\text{shift/esd})_{\text{max}} = -0.64$ . The maximum and minimum electron density in the final  $\Delta F$  map were 0.29 and  $-0.32 \text{ e } \text{\AA}^{-3}$ , respectively. The atomic scattering factors for all atoms were taken from SHELXL93 (SHELDRICK, 1993). The final atomic co-ordinates and equivalent isotropic displacement parameters for non-H atoms are given in Table 2. List of non-hydrogen atoms anisotropic displacement parameters and H-atom positions have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-139909. Selected geometrical parameters, (bond lengths and angles, torsion angles) are given in Tables 3 and 4 respectively.

Table 3: Bond lengths ( $\text{\AA}$ ) and angles ( $^\circ$ ) for non-H atoms (e.s.d.'s in parantheses)

C(1)-N(1)	1.503(7)	C(13)-C(14)	1.374(9)
C(1)-C(2)	1.551(9)	C(14)-C(15)	1.355(10)
C(2)-C(8)	1.525(8)	C(15)-C(16)	1.371(10)
C(2)-C(3)	1.526(9)	C(15)-Cl(1)	1.745(7)
C(3)-C(4)	1.532(9)	C(16)-C(17)	1.370(10)
C(3)-C(7)	1.535(9)	C(18)-C(19)	1.391(8)
C(4)-C(5)	1.552(9)	C(18)-C(26)	1.407(8)

C(5)-N(1)	1.495(7)	C(19)-C(20)	1.414(9)
C(6)-N(1)	1.495(7)	C(20)-N(2)	1.273(9)
C(6)-C(7)	1.536(10)	C(21)-N(2)	1.374(8)
C(8)-C(9)	1.503(10)	C(21)-C(22)	1.414(9)
C(10)-O(1)	1.442(6)	C(21)-C(26)	1.432(7)
C(10)-C(18)	1.520(7)	C(11)-O(2)	1.210(7)
C(11)-O(1)	1.368(6)	C(22)-C(23)	1.344(10)
C(11)-C(12)	1.454(8)	C(23)-C(24)	1.409(9)
C(12)-C(17)	1.376(8)	C(24)-C(25)	1.358(8)
C(12)-C(13)	1.398(7)	C(24)-O(3)	1.366(8)
C(25)-C(26)	1.426(8)	C(27)-O(3)	1.433(8)
C(5)-C(10)	1.532(7)		
C(8)-C(2)-C(1)	111.9(6)	C(15)-C(16)-C(17)	119.2(7)
C(3)-C(2)-C(1)	107.5(5)	C(16)-C(17)-C(12)	120.8(6)
C(2)-C(3)-C(4)	111.0(5)	C(19)-C(18)-C(26)	118.8(5)
C(2)-C(3)-C(7)	109.7(6)	C(19)-C(18)-C(10)	118.1(6)
C(4)-C(3)-C(7)	109.1(6)	C(26)-C(18)-C(10)	123.0(5)
C(3)-C(4)-C(5)	108.9(5)	C(18)-C(19)-C(20)	118.7(6)
N(1)-C(5)-C(10)	113.1(4)	N(2)-C(20)-C(19)	125.2(7)
N(1)-C(5)-C(4)	108.0(5)	N(2)-C(21)-C(22)	118.4(5)
C(10)-C(5)-C(4)	115.2(5)	N(2)-C(21)-C(26)	123.4(5)
N(1)-C(6)-C(7)	110.1(5)	C(3)-C(7)-C(6)	107.6(6)
C(9)-C(8)-C(2)	113.0(6)	C(22)-C(21)-C(26)	118.2(6)
O(1)-C(10)-C(18)	111.5(4)	C(23)-C(22)-C(21)	122.3(6)
O(1)-C(10)-C(5)	108.2(4)	C(22)-C(23)-C(24)	119.1(6)
C(18)-C(10)-C(5)	108.5(4)	C(25)-C(24)-O(3)	124.7(6)
O(2)-C(11)-O(1)	120.7(5)	C(25)-C(24)-C(23)	121.9(6)
O(2)-C(11)-C(12)	126.4(5)	O(3)-C(24)-C(23)	113.3(6)
O(1)-C(11)-C(12)	112.8(5)	C(24)-C(25)-C(26)	119.7(5)
C(24)-C(25)-C(26)	119.7(5)	C(17)-C(12)-C(13)	118.7(6)
C(18)-C(26)-C(25)	124.8(5)	C(6)-N(1)-C(1)	109.8(4)
C(18)-C(26)-C(21)	116.6(5)	C(5)-N(1)-C(1)	108.6(4)
C(25)-C(26)-C(21)	118.6(5)	C(20)-N(2)-C(21)	117.3(5)
C(6)-N(1)-C(5)	113.4(5)	C(11)-O(1)-C(10)	116.5(4)
N(1)-C(1)-C(2)	109.6(5)	C(8)-C(2)-C(3)	113.2(5)
C(24)-O(3)-C(27)	118.3(5)		
C(16)-C(15)-C(1)	119.2(6)		

Table 4: Comparison of selected torsion angles in the title compound(A), Cinchonine alkaloids(B), (cinchoninium)<sup>2+</sup>cation(C), dihydro epi-quinidine(D) and quinine salt of ferrocenecarboxylic acid (E)

	A	B	C	D	E
(a) About the C(10)-C(5) bond					
N(1)-C(5)-C(10)-C(18)	151.5(5)	-160.3	-167.3	-171.6	171.4
C(18)-C(10)-C(5)-C(4)	-83.6(6)	73.0	69.8	65.5	49.4
O(1)-C(10)-C(5)-C(4)	37.5(6)	-50.6	-48.4	-167.9	-73.8
O(1)-C(10)-C(5)-N(1)	-87.4(6)	76.1	74.5	-45.0	48.3
O(1)-C(10)-C(5)-H(5)	155.7(5)	-171.8	-175.3	-	-

(b) About the C(10)-C(18) bond					
O(1)-C(10)-C(18)-C(26)	141.1(5)	-158.7	-158.8	-37.6	-166.4
O(1)-C(10)-C(18)-C(19)	-42.0(6)	23.4	23.2	137.9	17.8
C(5)-C(10)-C(18)-C(19)	77.1(6)	-99.8	-97.0	-101.8	-109.2
C(5)-C(10)-C(18)-C(26)	-99.9(6)	78.1	80.9	82.7	66.5
(c) About the line C(3)-N(1)					
C(2)-C(3)-N(1)-C(1)	1.3(4)	9.1	12.5	10.8	9.5
C(2)-C(3)-N(1)-C(5)	118.6(5)	132.0	136.2	133.4	135.8
C(2)-C(3)-N(1)-C(6)	-118.3(5)	-110.0	-107.5	-107.9	-110.9
C(4)-C(3)-N(1)-C(5)	-2.8(4)	11.0	14.0	12.1	14.9
C(4)-C(3)-N(1)-C(6)	120.4(5)	129.0	129.3	130.7	128.1
C(4)-C(3)-N(1)-C(1)	-120.1(5)	-111.9	-109.7	-110.6	-111.4
C(7)-C(3)-N(1)-C(6)	1.1(4)	9.1	12.5	10.6	6.8
C(7)-C(3)-N(1)-C(1)	120.6(5)	128.2	130.9	129.3	127.3
C(7)-C(3)-N(1)-C(5)	-122.1(5)	-108.9	-105.3	-108.0	-106.4

References: (A) Present work. (B) OLEKSYN et al., 1979. (C) OLEKSYN et al., 1978. (D) CHEKHOV et al., 1974. (E) CARTER et al., 1967.

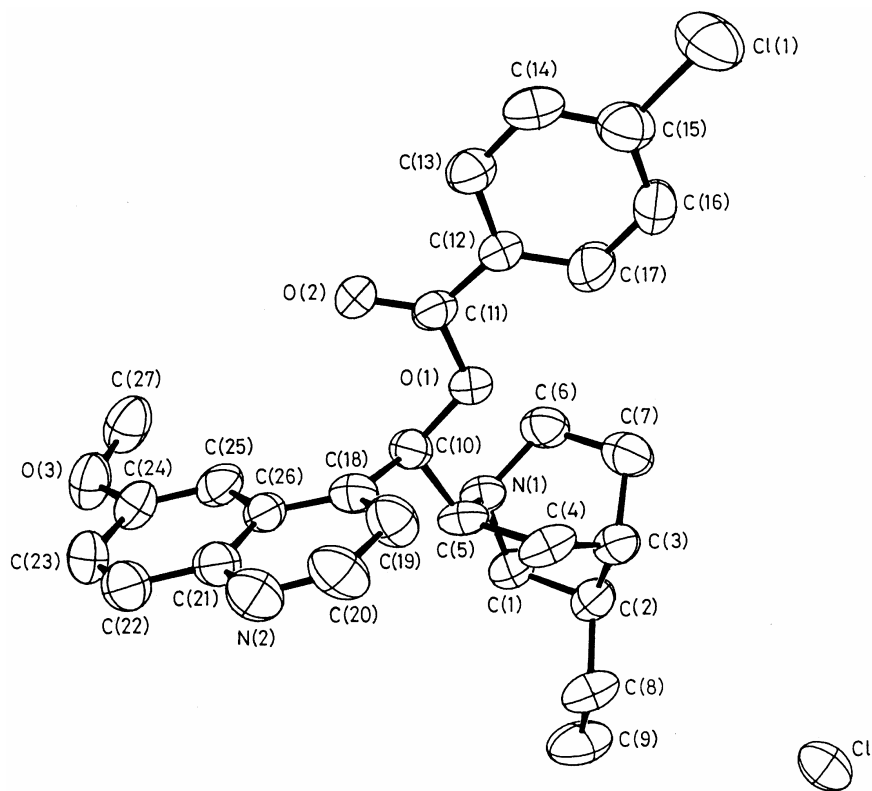


Fig. 1: Molecular structure Showing 50% probability displacement ellipsoids and hydrogen atoms are represented by spheres of arbitrary size.

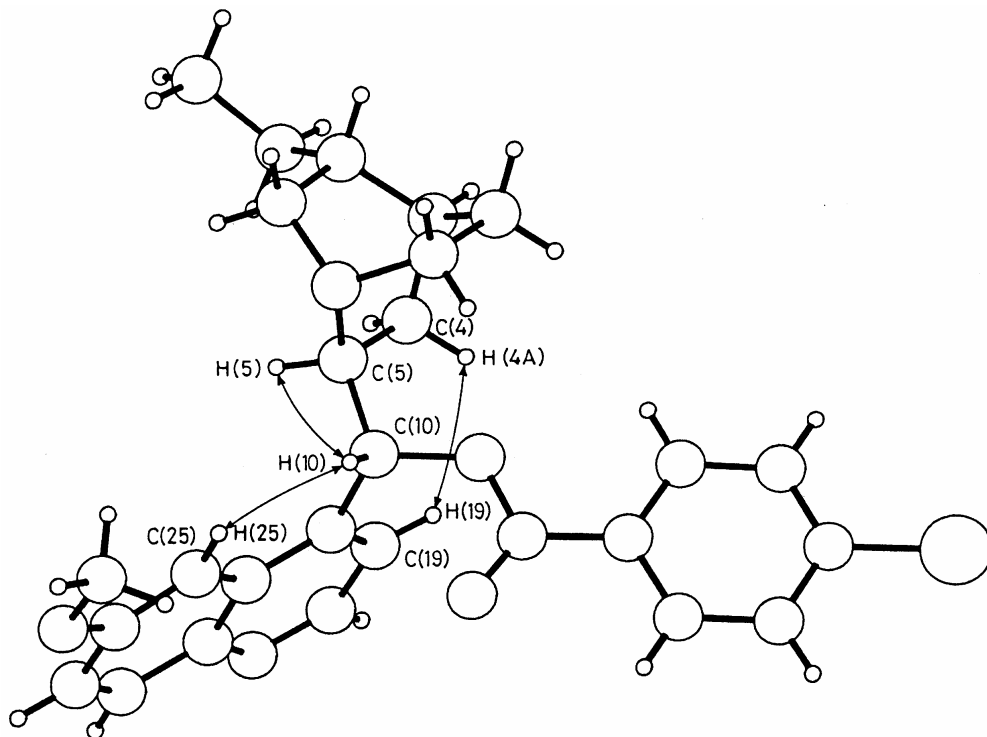


Fig. 2: The stick and ball model of the molecule showing open conformation

Table 5: Anisotropic displacement parameters ( $\times 10^3$ ) for non-H atoms

Atom	$U_{11}$	$U_{22}$	$U_{33}$	$U_{23}$	$U_{13}$	$U_{12}$
C(1)	47(3)	60(3)	54(3)	-5(3)	-7(3)	0(3)
C(2)	49(3)	67(4)	47(3)	-1(3)	-2(3)	9(3)
C(3)	44(3)	58(4)	71(4)	4(3)	-2(3)	2(3)
C(4)	43(3)	71(4)	68(4)	-21(3)	-14(3)	10(3)
C(5)	30(2)	65(4)	58(3)	-7(3)	3(2)	1(2)
C(6)	43(3)	74(4)	59(3)	-1(3)	10(3)	0(3)
C(7)	54(3)	73(4)	101(5)	16(4)	14(4)	-5(4)
C(8)	44(3)	78(4)	77(4)	-19(4)	-15(3)	8(3)
C(9)	57(4)	95(6)	27(7)	-21(6)	-25(5)	-13(4)
C(10)	41(2)	48(3)	47(3)	1(2)	2(2)	-4(2)
C(11)	33(2)	63(3)	50(3)	5(3)	-3(2)	3(3)
C(12)	36(2)	54(3)	51(3)	5(3)	-5(2)	0(2)
C(13)	48(3)	54(3)	57(3)	-3(3)	-8(3)	-1(3)
C(14)	45(3)	70(4)	69(4)	-15(3)	-12(3)	-7(3)
C(15)	58(3)	58(4)	83(4)	-4(4)	-3(4)	-8(3)
C(16)	86(5)	80(5)	104(6)	48(5)	-43(5)	-26(4)
C(17)	73(4)	65(4)	86(5)	18(4)	-36(4)	-18(4)

C(18)	37(2)	57(3)	52(3)	-5(3)	4(2)	-1(3)
C(19)	62(4)	56(4)	67(4)	2(3)	19(3)	4(3)
C(20)	66(4)	72(4)	74(4)	-7(4)	30(4)	0(4)
C(21)	46(3)	58(3)	50(3)	0(3)	-1(3)	-1(3)
C(22)	59(3)	96(5)	45(3)	5(4)	5(3)	-2(4)
C(23)	70(4)	78(4)	45(3)	15(3)	-5(3)	-2(4)
C(24)	59(3)	66(4)	48(3)	4(3)	-14(3)	5(3)
C(25)	45(3)	75(4)	43(3)	-3(3)	-8(2)	4(3)
C(26)	38(2)	50(3)	43(3)	0(2)	-2(2)	2(2)
C(27)	76(4)	78(5)	79(4)	9(4)	-9(4)	27(4)
N(1)	39(2)	55(3)	51(2)	-7(2)	3(2)	3(2)
N(2)	61(3)	76(4)	66(3)	-2(3)	6(3)	-1(3)
O(1)	37(2)	53(2)	53(2)	6(2)	-7(2)	-7(2)
O(2)	45(2)	72(3)	70(3)	28(2)	-16(2)	-7(2)
O(3)	82(3)	63(3)	65(3)	15(2)	-5(3)	19(2)
Cl(1)	86(1)	68(1)	142(2)	7(1)	-6(1)	-29(1)
Cl(2)	70(1)	67(1)	62(1)	-8(1)	21(1)	-13(1)

The anisotropic displacement factor exponent takes the form:  $-2\pi^2 [h^2 a^{*2} U_{11} + \dots + 2 h k a^* b^* U_{12}]$

Table 6: Hydrogen co-ordinates ( $\times 10^3$ ) and isotropic displacement parameters ( $\text{\AA}^2 \times 10^3$ ).

Atom	x	y	z	$U_{eq}$
H(1A)	3935	8641	7709	67
H(1B)	4726	8660	6974	67
H(2)	4756	7175	8144	67
H(3)	4665	5556	7409	67
H(4A)	3874	5622	6141	67
H(4B)	5051	6229	6161	67
H(5)	4277	7769	5863	67
H(6A)	1768	6997	6930	67
H(6B)	2155	7597	7688	67
H(7A)	3003	6110	8081	67
H(7B)	2649	5520	7309	67
H(8A)	6463	6562	7539	67
H(8B)	6220	7352	6848	67
H(9A)	7514	8136	7693	116
H(9B)	6638	8037	8375	116
H(9C)	6394	8827	7683	116
H(10)	2252	7766	5450	67
H(13)	-294	4945	4332	67
H(14)	-1154	3290	4539	67
H(16)	871	2773	6353	67
H(17)	1698	4445	6180	67
H(19)	3910	5572	4755	67
H(20)	4972	5545	3624	67
H(22)	4724	8767	2553	67

H(23)	3792	10341	2775	67
H(25)	2421	9129	4724	67
H(27A)	1292	11690	4370	116
H(27B)	1949	10873	4903	116
H(27C)	1002	10452	4338	116
H(Cl)	742(6)	438(6)	829(5)	67

#### 4. Discussion

The molecular structure of the cinchonan alkaloid is shown in Fig. 1. Its conformation is very close to alkaloids like cinchonine (OLEKSYN et al., 1979) and (cinchoninium)<sup>2+</sup> cation in its tetrachlorocadmate (OLEKSYN, STADNICKA and HODOROWICZ, 1978). In comparison with alkaloids like (+)-10-bromo-10-11-dihydroepiquinidine (CHEKHLOV, et al., 1974) and quinidine and its salt with (-)-1,1-dimethyl-3-ferrocenecarboxylic acid (CARTER et al., 1967) the torsion angles differ slightly. A list of relevant torsion angles are given in Table 4 for some alkaloids showing the similarity.

The bond lengths and angles in the quinoline ring systems are very close to those determined in 2-quinoline carboxamide (GDANIEC et al., 1977), biquinolyl (LENNER and LINDGREN, 1976) and 8-quinolyl cyanomethyl sulphone (HARLOW and SIMONSEN, 1978) except C(20)—N(2) [1.273(9) Å] distance. The C—C distance ranges from 1.344(10) to 1.426(8) Å and the C—N distances in this ring system are unequal [C(20)—N(2) 1.273(9) and N(2)—C(21) 1.374(8) Å] due to different environment of carbon atoms and these values are close to the unprotonated iodoform-quinoline (BJORVATTEN and HASSEL, 1962). The bond angle C(20)—N(2)—C(21) 117.3(5)° is similar to that in the afore said compounds, but this value is 5° less than the corresponding angles in diprotonated cinchonine (OLEKSYN, et al., 1978). This angle deformation is due to repulsive interaction between the free electron pair at N(2). This effect increases the adjacent bond angles C(19)—C(20)—N(2) [125.2(7)°] and C(26)—C(21)—N(2) [123.4(5)°] and shortens the bond distances of N(2)—C(21) [1.374(8) Å] and N(2)—C(20) [1.273(9) Å]. Similar effects were reported by OLEKSYN et al., 1979, GIEREN and SCHANDA, 1977.

In the quinuclidine ring system the C—N distances [N(1)—C(1) 1.503(7) and N(1)—C(6) 1.495(7) Å] are slightly longer compared with cinchonine alkaloid (OLEKSYN et al., 1979). No significant difference was found in the bond lengths, on comparing with alkaloid cinchonine and protonated quinuclidine (OLEKSYN et al., 1978). But the bond angle C(5)—N(1)—C(6) [113.4(5)°] is varied because of the change of repulsive interaction between the lone pair electrons at N(1) and electrons in the N(1)—C(5), N(1)—C(6) and N(1)—C(1) bonds. A co-operative effect is connected with the change of the electron density along these bonds. The lone pair at N(1) diminishes the electron density in the vicinity of N(1) thus reducing the repulsion between the electrons of the bonds N(1)—C(6), N(1)—C(5) and N(1)—C(1). This leads to a more tetrahedral arrangement of the bonds around N(1) in comparison to the slightly flattened tetrahedron observed in the protonated quinuclidine. The same effect is reported in Cinchonine alkaloid (OLEKSYN et al., 1979).

The overall conformation of the title compound is determined by the torsion angles of the bonds C(5)—C(10) and C(10)—C(18) bond. These bonds link the two rigid quinuclidine and quinoline ring systems, thus defining the spatial relationship between them. The spatial arrangement and torsion angles show the open conformation of the alkaloid (DIJKSTRA et al., 1989). This is evident by the torsion angles C(19)—C(18)—C(10)—C(5) [77.0(6)°] and H(10)—C(10)—C(5)—H(5) [-85.0(6)°]. The Fig. 2. describes the close spatial arrangement of the hydrogen atoms H(5), H(10), H(25), H(4A) and H(19) with the interatomic distances 2.12 Å [H(25)···H(10)], 2.48 Å [H(5)···H(10)] and 3.38 Å [H(5)···H(25) and 2.39 Å [H(4A)···H(19)].

The molecular packing is predominantly stabilized by hydrogen bonding. The HCl molecule interact with N(1) forming an intermolecular hydrogen bond Cl—H(Cl)···N(1<sup>i</sup>). Its geometrical parameters are Cl—H(Cl) 1.09(7) Å, Cl···N(1<sup>i</sup>) 2.951(3), H(Cl)···N(1<sup>i</sup>) 2.019(5) Å and Cl—H(Cl)···N(1<sup>i</sup>) 173.4(3)° [symmetry code i = 1-x, -1/2+y, 3/2-z].

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