
Silver forms with the major alkaloids of cinchona bark — quinine, quinidine, cinchonine and cinchonidine — complexes of the types MHL, ML, M_2L_2 , M_2L and M_3L_2 . Stability constants of these complexes, determined by potentiometric titrations, are discussed in relation to the stereochemical configuration of the alkaloids.

SILVER COMPLEXES OF CINCHONA ALKALOIDS

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1 — INTRODUCTION

In a previous work (1) we have shown that silver forms with quinine a series of complexes corresponding to the formulae MHL, ML, M_2L and M_2L_2 , and we have determined the stability constants of these species.

The formation of the different complexes depends on the particular conformation of the ligand and it seemed of interest to study the variation of stability in analogous complexes formed by the other major alkaloids of the cinchona bark, e.g., quinidine, cinchonine and cinchonidine.

Larger differences are, in principle, to be expected for the complexes of quinine and cinchonidine on one hand, and of cinchonine and quinidine on the other. Indeed, the absolute configuration of these alkaloids has already been determined and it was confirmed that quinine is methoxycinchonidine and quinidine is methoxycinchonine (2).

However, even within each pair of substances, some differences are also to be expected, because the methoxyl grouping will affect the basicity of the quinolinic nitrogen atom in the molecule of the alkaloids, thereby altering its coordinating ability.

In the present work we report values for the stability constants of all the silver complexes formed with each of the four alkaloids and discuss the variations observed in the results.

2 — EXPERIMENTAL

2.1 — REAGENTS

All the products used were of analytical grade. The alkaloids were dissolved in 1000×10^{-3} M sulphuric acid to give 10^{-3} M solutions of the species H_2L^{2+} (where L stands for the molecule of the respective alkaloids); in the case of quinine its acid sulfate is available so it was simply dissolved in water.

Carbonate-free potassium hydroxide was prepared according to the instructions of SCHWARZENBACH and BIEDERMAN (3).

Its ionic strength was made up to 0.100 M in potassium nitrate to take into account the neutralization of hydroxide and hydrogen ions which occurs in the titrations.

All the water used was de-ionised, e.g., distilled water passed through an Elgastat mixed bed ion-exchange resin.

2.2 — TECHNIQUE

Dissociation constants of the H_2L^{2+} ions and the stability constants of the complexes of general formula $Ag_xH_yL_z$ were determined by potentiometric titrations using a glass electrode (Radiometer G 2025 B) in a double walled vessel maintained at

20.0°C with circulating water pumped from a thermostat bath.

A saturated calomel used as reference was placed in a similar but smaller vessel connected to the first through a kind of Laitinen bridge of saturated KNO_3 (4).

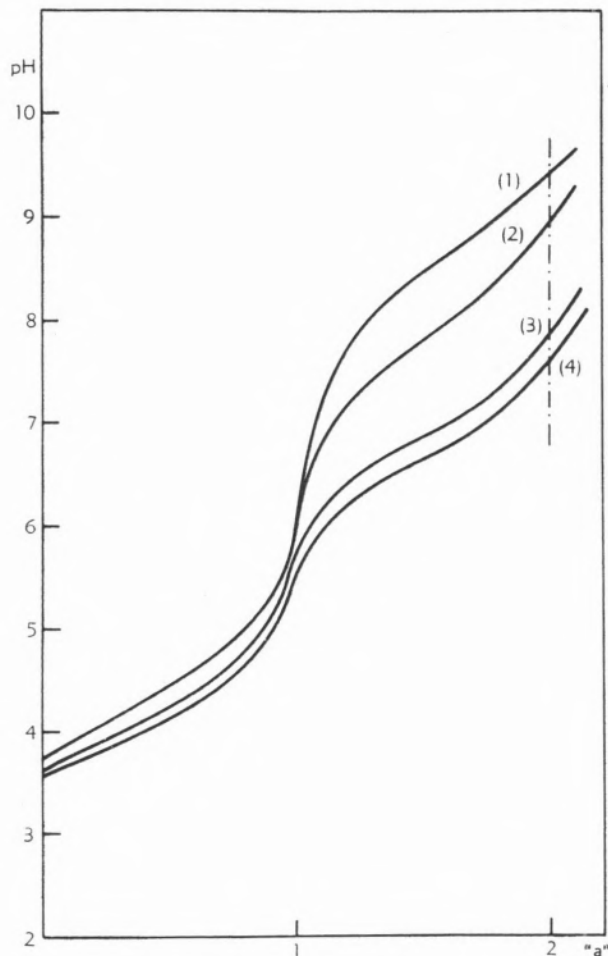


Fig. 1—Titration curves of quininium sulfate alone and in the presence of silver

- (1) Ligand alone; (2) $C_M/C_L=1$;
(3) $C_M/C_L=10$; (4) $C_M/C_L=20$.

The pH meter (Radiometer pHM4) was calibrated as a concentration probe by titrating perchloric, acetic and ethylene-diaminetetracetic acids and standardized each time with 0.050 M potassium hydrogen phthalate.

The solutions to be titrated were made up by taking 100.0 ml of the solution of the ligand, concentration C_L , and adding 10.0 ml of the solution of the metal salt, concentration C_M , and 10.0 ml of a potassium

nitrate solution, concentration such as to give a final ionic strength of 0.100 M. The initial total volume was thus 120.0 ml.

A more detailed description has been given elsewhere (5).

Three or four sets of titrations were performed in

Table I

TITRATIONS OF CINCHONINE BISULFATE

$$C_L=1.015 \times 10^{-3} \text{ M}; C_B=0.099 \text{ M}$$

Volume of KOH	pH			
	C_M			
v ml	0	1.000×10^{-2}	1.000×10^{-1}	2.000×10^{-1}
0.00	3.682	3.677	3.604	3.558
0.10	3.802	3.781	3.690	3.627
0.20	3.916	3.897	3.787	3.716
0.30	4.037	4.020	3.887	3.807
0.40	4.167	4.144	3.998	3.887
0.50	4.305	4.281	4.121	3.997
0.60	4.455	4.826	4.261	4.128
0.70	4.635	4.597	4.422	4.290
0.80	4.841	4.810	4.631	4.486
0.90	5.168	5.110	4.942	4.797
1.00	5.840	5.811	5.663	5.485
1.10	7.532	7.266	6.641	6.443
1.20	7.968	7.632	6.925	6.724
1.30	8.237	7.850	7.092	6.895
1.40	8.451	8.041	7.241	7.038
1.50	8.622	8.217	7.382	7.178
1.60	8.798	8.388	7.513	7.307
1.70	8.986	8.564	7.672	7.467
1.80	9.163	8.770	7.850	7.635
1.90	9.357	9.006	8.081	7.847
2.00	9.593	9.321	8.302	8.015

each case. In the following tables the experimental results obtained in one of these sets are presented. In fig. 1 a set of titration curves is also presented.

2.3 — CALCULATIONS

The method used was described in a previous paper (1); a more detailed treatment is now presented.

It is based on the consideration of all the species which may be present during the titrations:

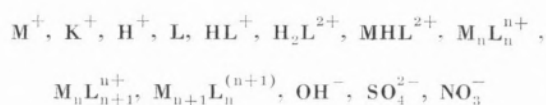


Table II

TITRATIONS OF QUININE BISULFATE

$$C_L = 1.015 \times 10^{-3} \text{ M}; C_B = 0.099 \text{ M}$$

Volume of KOH	pH		
	C_M		
v ml	1.000×10^{-2}	1.000×10^{-1}	2.000×10^{-1}
0.00	3.729	3.634	3.568
0.10	3.852	3.740	3.666
0.20	3.981	3.847	3.755
0.30	4.121	3.970	3.863
0.40	4.252	4.089	3.977
0.50	4.393	4.220	4.101
0.60	4.549	4.362	4.233
0.70	4.715	4.536	4.399
0.80	4.921	4.733	4.607
0.90	5.227	5.039	4.901
1.00	5.904	5.613	5.466
1.10	6.861	6.165	5.976
1.20	7.203	6.403	6.210
1.30	7.421	6.573	6.369
1.40	7.607	6.709	6.502
1.50	7.780	6.834	6.631
1.60	7.963	6.970	6.767
1.70	8.164	7.111	6.912
1.80	8.386	7.275	7.082
1.90	8.616	7.502	7.301
2.00	8.961	7.841	7.641
2.10	—	8.301	7.991

Here M^+ corresponds to Ag^+ added the nitrate, and L corresponds to the several ligands, added as acid sulfates.

The species with $n > 2$ have only a limited possibility of existence, and, in the conditions used, the complexes $M_nL_{n+1}^{n+}$ are formed only in negligible amounts and can be disregarded in the calculations.

Considering all the remaining species, the total con-

centrations of the ligand and of the metal are given by

$$C_L = [L] + [HL^+] + [H_2L^{2+}] + [MHL^{2+}] + \\ + [ML^+] + 2[M_2L_2^{2+}] + [M_2L^{2+}] + 2[M_3L_2^{3+}] \quad (1)$$

Table III

TITRATIONS OF QUINIDINE BISULFATE

$$C_L = 1.000 \times 10^{-3} \text{ M}$$

$$* C_L = 1.012 \times 10^{-3} \text{ M}$$

$$C_B = 0.099 \text{ M}$$

$$C_B = 0.1065 \text{ M}$$

Volume of KOH	pH			
	C_M			
v ml	0	1.000×10^{-2}	1.000×10^{-1}	2.000×10^{-1}
0.00	3.799	3.797	3.705	3.635
0.10	3.940	3.926	3.808	3.731
0.20	4.092	4.066	3.923	3.834
0.30	4.241	4.208	4.044	3.940
0.40	4.394	4.353	4.165	4.059
0.50	4.558	4.501	4.305	4.162
0.60	4.737	4.663	4.460	4.339
0.70	4.939	4.845	4.643	4.456
0.80	5.221	5.083	4.793	4.673
0.90	5.763	5.444	5.225	4.997
1.00	7.372	6.320	6.000	5.744
1.10	7.931	7.236	6.532	6.340
1.20	8.222	7.538	6.757	6.574
1.30	8.443	7.745	6.916	6.735
1.40	8.631	7.932	7.060	6.875
1.50	8.805	8.102	7.151	7.009
1.60	8.984	8.276	7.333	7.148
1.70	9.182	8.475	7.486	7.300
1.80	9.393	8.628	—	7.494
1.90	9.629	8.890	—	—
2.00	9.863	—	—	—

$$C_M = [M^+] + [ML^+] + [MHL^{2+}] + 2[M_2L_2^{2+}] + \\ + 2[M_2L^{2+}] + 3[M_3L_2^{3+}] \quad (2)$$

From the electroneutrality condition

$$[M^+] + [H^+] + [K^+] + [HL^+] + 2[H_2L^{2+}] + \\ + [ML^+] + 2[MHL^{2+}] + 2[M_2L_2^{2+}] + \\ + 2[M_2L^{2+}] + 3[M_3L_2^{3+}] = [OH^-] + \\ + [NO_3^-] + 2[SO_4^{2-}] \quad (3)$$

But $[\text{NO}_3^-] = C_M$ and $[\text{SO}_4^{2-}] = C_L$, and defining «a» — degree of neutralization — as the number of equivalents of base added per mole of ligand, it follows that

$$[\text{K}^+] = a C_L \quad (4)$$

Table IV

TITRATIONS OF CINCHONIDINE BISULFATE

$$C_L = 1.005 \times 10^{-3} \text{ M}; C_B = 0.099 \text{ M}$$

Volume of KOH	pH			
	C_M			
v ml	0	1.000×10^{-2}	1.000×10^{-1}	2.000×10^{-1}
0.00	3.711	3.703	3.604	3.533
0.10	3.820	3.813	3.691	3.612
0.20	3.936	3.923	3.785	3.698
0.30	4.058	4.038	3.884	3.793
0.40	4.186	4.162	3.995	3.895
0.50	4.328	4.300	4.122	4.014
0.60	4.480	4.444	4.262	4.153
0.70	4.652	4.618	4.423	4.315
0.80	4.882	4.842	4.642	4.523
0.90	5.249	5.192	4.993	4.901
1.00	6.093	6.075	5.780	5.693
1.10	7.399	7.103	6.375	6.203
1.20	7.855	7.416	6.612	6.413
1.30	8.122	7.619	6.765	6.565
1.40	8.313	7.795	6.897	6.694
1.50	8.482	7.965	7.024	6.823
1.60	8.644	8.140	7.155	6.953
1.70	8.803	8.323	7.302	7.092
1.80	8.974	8.531	7.473	7.262
1.90	9.163	8.780	7.711	7.485
2.00	9.380	9.104	—	—

From (1), (2) and (3), replacing $[\text{NO}_3^-]$, $[\text{SO}_4^{2-}]$ and $[\text{K}^+]$ by their values:

$$(2-a) C_L - [\text{H}^+] + [\text{OH}^-] = 2 [\text{H}_2\text{L}^{2+}] + [\text{HL}^+] + [\text{MHL}^{2+}] \quad (5)$$

and

$$(2-a) C_L - [\text{H}^+] + [\text{OH}^-] = 2 \cdot \frac{[\text{H}^+]^2 [\text{L}]}{k_1^H \cdot k_2^H} +$$

$$+ \frac{[\text{H}^+] [\text{L}]}{k_2^H} + K_{\text{MHL}} \cdot \frac{[\text{M}^+] [\text{H}^+] [\text{L}]}{k_2^H}$$

where k_1^H are the dissociation constants of the species H_1L and $K_{\text{MHL}} = [\text{MHL}] / [\text{M}] [\text{HL}]$

The free ligand concentration will then be

$$[\text{L}] = \frac{(2-a) C_L - [\text{H}^+] + [\text{OH}^-]}{2 \cdot \frac{[\text{H}^+]^2}{k_1^H \cdot k_2^H} + \frac{[\text{H}^+]}{k_2^H} + K_{\text{MHL}} \cdot [\text{M}^+] \cdot \frac{[\text{H}^+]}{k_2^H}} \quad (6)$$

which may frequently be simplified to

$$[\text{L}] = \frac{(2-a) C_L - [\text{H}^+] + [\text{OH}^-]}{\frac{[\text{H}^+]}{k_2^H} (1 + K_{\text{MHL}} [\text{M}^+])} \quad (7)$$

The free ligand concentration may then be calculated if the k_1^H , the free metal concentration, the stability constant of the protonated complex and the pH of the solution are known.

Normally, this problem can only be solved by an iterative procedure, unless the free metal concentration is held approximately constant. This can be achieved using a large excess of the metal salt or equilibrating the solution with one of its sparingly soluble precipitates (5).

On the other hand, the stability constant of the protonated complex can easily be calculated when MHL is the only complex species containing M in a certain buffer region. For the purpose it is enough to determine a «conditional dissociation constant» of the ligand acid on that region.

The true dissociation constant is, without regard to the charges,

$$k_1 = \frac{[\text{H}] [\text{HL}]}{[\text{H}_2\text{L}]} \quad (8)$$

And the total concentration of ligand is

$$C_L = [\text{HL}] + [\text{H}_2\text{L}] + [\text{MHL}]$$

or

$$[\text{HL}] = C_L - [\text{H}_2\text{L}] - [\text{MHL}] \quad (9)$$

Hence

$$k_1 = \frac{[H] \{ C_L - [H_2L] - [MHL] \}}{[H_2L]}$$

$$= \frac{[H] C_L}{[H_2L]} - [H] - \frac{[MHL] [H]}{[H_2L]} \quad (10)$$

If the apparent dissociation constant k'_1 has been determined ignoring MHL, its value will be

$$k'_1 = \frac{[H] C_L}{[H_2L]} - [H]$$

or

$$k_1 = k'_1 - \frac{[MHL] [H]}{[H_2L]} \quad (11)$$

Introducing K_{MHL} , it results:

$$k_1 = k'_1 - K_{MHL} \cdot \frac{[M] [H] [LH]}{[H_2L]}$$

or

$$k_1 = k'_1 - K_{MHL} \cdot k_1 \cdot [M] \quad (12)$$

This is equivalent to

$$k_1 (1 + K_{MHL} [M]) = k'_1 \quad (13)$$

Hence

$$\frac{k'_1}{k_1} = 1 + K_{MHL} [M]$$

and

$$pk_1 - pk'_1 = \log (1 + K_{MHL} \cdot [M]) \quad (14)$$

This expression results also directly from the definition of «conditional dissociation constant» and allows K_{MHL} to be calculated if $[M]$ is held nearly constant, simply by determining the dissociation constant of the acid ligand on those conditions.

The deduction may now be continued, as follows:

From (1)

$$C_L - \alpha [L] = [MHL] + [ML] + 2 [M_2L_2] + [M_3L_2] + 2 [M_2L]$$

where

$$\alpha = 1 + \frac{[H^+]}{k_2^H} + \frac{[H^+]^2}{k_1^H k_2^H}$$

Hence

$$C_L - \alpha [L] = K_{MHL} \cdot \frac{[M] [H] [L]}{k_2^H} + [M] [L] K_{ML} + 2 \beta_{22} [M]^2 [L]^2 + \beta_{21} [M]^2 [L] + 2 \beta_{32} [M]^3 [L]^2 \quad (15)$$

Or, dividing by $[M] [L]$ and rearranging,

$$\frac{C_L - \alpha [L]}{[M] [L]} - K_{MHL} \cdot \frac{[H]}{k_2^H} = K_{ML} + \beta_{21} [M] + \{ 2 \beta_{22} [M] + 2 \beta_{32} [M]^2 \} [L] \quad (16)$$

where

$$K_{ML} = [ML] / [M] [L]$$

$$\beta_{21} = [M_2L] / [M]^2 [L]$$

$$\beta_{22} = [M_2L_2] / [M]^2 [L]^2$$

$$\beta_{32} = [M_3L_2] / [M]^3 [L]^2$$

If species with $n > 2$ are taken into account, a general equation analogous to (16) is obtained:

$$\frac{C_L - \alpha [L]}{[M] [L]} - K_{MHL} \cdot \frac{[H]}{k_2^H} = \sum_{n=1}^{\infty} n [M]^{n-1} [L]^{n-1} \{ \beta_{nn} + \beta_{(n+1)n} [M] + \beta_{n(n+1)} [L] \} \quad (17)$$

where

$$\beta_{11} = K_{ML}$$

Now, if $[M]$ is held approximately constant, as in the case of the 10 : 1 and 20 : 1 titrations (tables I-IV) plots of

$$K = \frac{C_L - \alpha [L]}{[M] [L]} - K_{MHL} \cdot \frac{[H]}{k_2^H}$$

against $[L]$ give straight lines, when the species with $n > 2$ can be disregarded, which is the case.

The intercepts and the slopes of these lines are cal-

culated by the least squares method allowing the establishment of a system of equations which can be solved unequally for K_{ML} , β_{21} , β_{22} and β_{32} .

If curves were obtained instead of straight lines species with $n > 2$ would have to be taken into account. The value used for $[M]$ can be, in a first approximation, equal to $C_M - C_L$, being refined afterwards if wanted, although the correction does not affect appreciably the results.

For the 1:1 titrations $[M]$, cannot be considered as constant but, on the other hand, complexes M_2L and M_3L_2 may also be disregarded since the amount of metal in solution is not sufficient for their formation be significative. K values may then be plotted against $[M]$ $[L]$ values, refined by successive approximations.

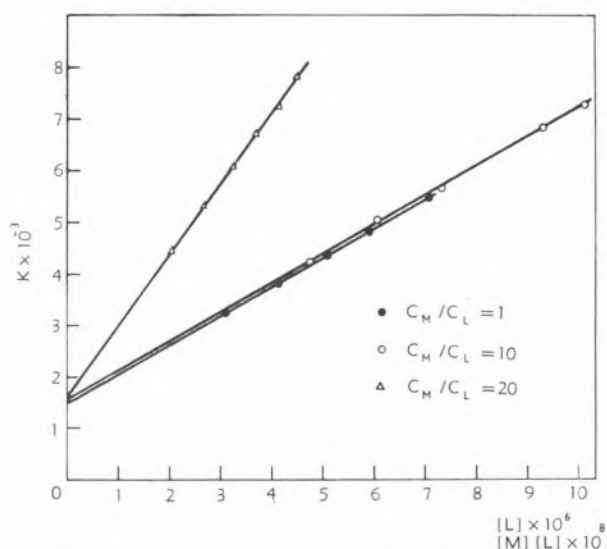


Fig. 2—Plots of K against $[L]$ and $[M] [L]$ (equation 16) on titrations of quinidinium sulfate

Straight lines are again obtained, the intersect giving K_{ML} and the slope being equal to $2\beta_{22}$.

This method yields the stability constants of all the predominant species in solution and it affords, at the same time, a demonstration of their presence and justification for excluding species with $n > 2$ in the general formula.

Some examples of the plots mentioned above are given in fig. 2.

3—RESULTS AND DISCUSSION

The dissociation constants of the H_2L^{2+} species, where L represents the molecule of the neutral alka-

loid, were calculated by the usual methods; the stability constants of the various silver complexes were obtained by the method just described. The results are summarized in table v.

The standard deviations for the values of the logarithms of the dissociation constants are ± 0.01 for each titration and ± 0.03 for a set of titrations; for the values of the stability constants the standard

Table V

STABILITY CONSTANTS OF PROTON AND SILVER COMPLEXES OF THE CINCHONA ALKALOIDS

$T=20.0^\circ C$; $\mu=0.1 M (KNO_3)$

Species		Cincho- nine	Quini- dine	Quinine	Cincho- nidine
H_2L^{2+}	pk_1^H	4.22	4.46	4.36	4.24
HL^+	pk_2^H	8.70	8.68	8.51	8.52
$AgHL$	$\log K_{MHL}$	2.02	2.00	1.98	2.04
AgL	$\log K_{ML}$	3.13	3.13	3.10	3.10
Ag_2L	$\log \beta_{21}$	3.86	3.80	4.46	4.20
Ag_2L_2	$\log \beta_{22}$	10.2	10.56	10.94	10.66
Ag_3L_2	$\log \beta_{32}$	11.7	11.95	12.45	12.28

deviations are, in general, smaller than ± 0.05 ; only in some cases is of the order of ± 0.1 .

The results presented for quinine are only slightly different from those published before (1); the differences are due to the fact that the new values are averages of several sets of titrations (three at least). As it can be seen, a value for β_{32} could now be obtained; the concentration of M_3L_2 is small compared with that of M_2L_2 or M_3L , explaining why no sensible errors result when that species is not taken into account.

The values obtained for the dissociation constants do not require further discussion; pk_1 corresponds to the ionization of the quinolinium proton, whereas pk_2 corresponds to the ionization of the proton bonded to the nitrogen atom of the quinuclidyl moiety.

For the stability constants two trends are apparent: on one hand, the values obtained for the M_2L , M_2L_2 and M_3L_2 complexes of quinine and cinchonidine are

higher than those obtained for cinchonine and quinidine; on the other hand, the values for the complexes of quinine are higher than those for the complexes of quinidine and the values for the complexes of cinchonidine are higher than those for the complexes of cinchonine.

If one recalls the structure of these alkaloids (fig. 3) some similarities of behaviour will readily be understood.

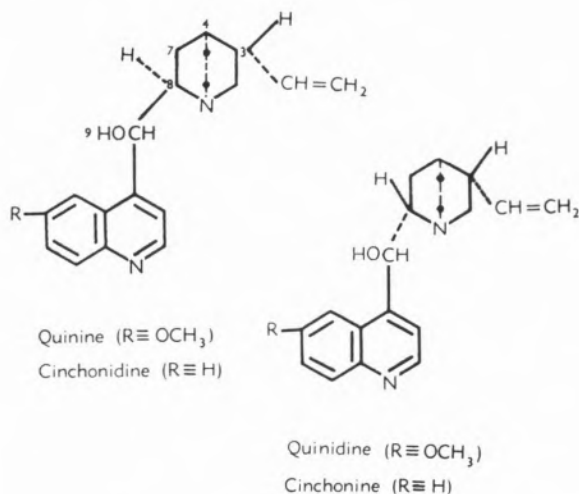


Fig. 3—Conformation at C(8) of the major alkaloids of the cinchona bark

Indeed, quinine and cinchonidine have the same configuration and the same happens for quinidine and cinchonine. The difference within each pair of alkaloids is a methoxyl group in the quinolinyl nucleus. This will affect the basicity of the quinolinic nitrogen atom but will not influence the stereochemistry of the complexes. One would then expect the values of pk_1 for quinine and quinidine to be similar as for the pair cinchonine-cinchonidine. The values presented in table v show how closely this expectation is followed.

Since the values for the stability constants of the protonated complexes are closely related to the values of pk_1 , it is not surprising, either, that they are also so similar.

For pk_2 it appears that these values are influenced by the conformation at the carbon atoms $\text{C}_{(8)}$ and $\text{C}_{(9)}$ although the reason for the fact cannot be conclusively demonstrated (6).

The comparisons must then be established between quinine and cinchonidine, on one hand, and quinidine and cinchonine, on the other. The values summarized in table v show again how closely the experimental data follows the theoretical prediction — pk_2 values for quinine and cinchonidine are 8.51 and 8.52, and for quinidine and cinchonine are 8.68 and 8.70.

The normal ML complexes follow the expected trend, in agreement with the values of pk_2 , although it is

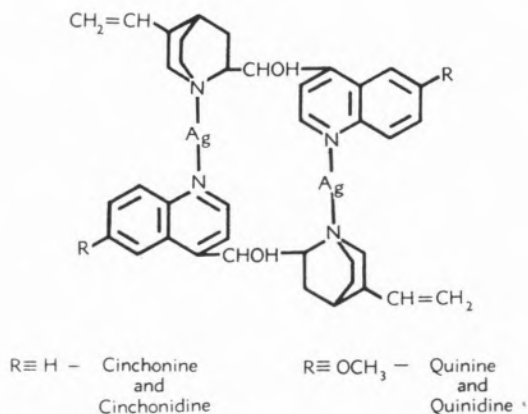


Fig. 4—Structural formula of the M_2L_2 complexes

difficult to understand why an increase of 0.2 logarithmic units in the value of pk_2 for cinchonine and quinidine leads to an increase of only 0.03 logarithmic units in the stability constants of the normal complexes of these substances.

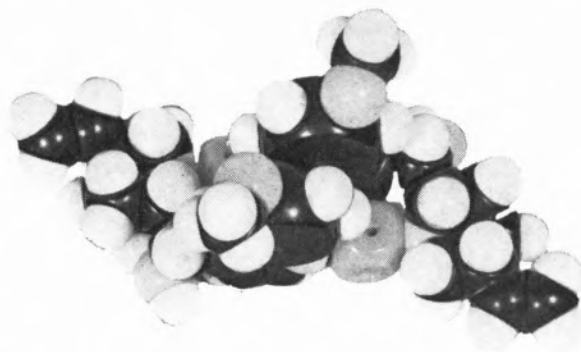


Fig. 5—Molecular model of the Ag_2L_2 complex; L stands for the quinine molecule

Perhaps even more disturbing are the considerable differences verified in $\log \beta_{21}$ values, in favour of the complexes of quinine and cinchonidine, relatively to the analogous complexes of the two alkaloids. The

values obtained were, however, reproducible in several sets of titrations and although the accuracy of the experimental data and the complexity of the calculations may cause some error, the differences found correspond probably to intrinsic differences in the complexes, suggesting that the orientation of the two nitrogen atoms, in the molecule of the ligand, relatively to each other, is not indifferent.

For the M_2L_2 complexes a similar occurrence is found but it can be verified using molecular models, that it is indeed slightly easier for quinine and cinchonidine to adopt the conformation required for the formation of such complexes (fig. 4). This results from the particular conformation of the alkaloids at the carbon atom $C_{(9)}$ (see ref. 2).

We have already shown that the M_2L_2 complexes were predominant in solution, at least above pH7 (1). Their formation is easy due to the tendency of silver to linear coordination and molecular models (fig. 5) show also that no internal tensions are originated in the molecules of the ligands.

The formation of M_3L_2 corresponds to opening the ring of the M_2L_2 complexes which take up a further Ag^+ ion. The concentration of these species is accordingly almost negligible and the same happens, by majority of reason, for higher complexes ($n > 2$, in the general formula).

The results obtained in this work show that the conformation of the alkaloids studied does not affect appreciably the stabilities of the complexes which they form with silver.

The differences observed are reduced and may be partially due to small experimental errors to which the method of computation is rather sensitive.

In particular the new experiments do not throw further light on the problem of the «protection» of colloidal silver halogenides discussed in the previous paper (1).

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RESUMO

A prata forma com os alcalóides principais do grupo da quina — quinino, quinidina, cinchonina e cinchonidina — complexos dos tipos MHL , ML , M_2L_2 , M_2L e M_3L_2 . Determinaram-se por potenciométria as constantes de estabilidade desses complexos, relacionando-se as diferenças observadas com a configuração estereoquímica dos alcalóides.