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ROTATORY DISPERSION STUDIES—V

THE CINCHONA ALKALOIDS[1]

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Abstract—The ORD curves of some alkaloids of the cinchona family and their 9-chloro-9-deoxy, 9-deoxy-, 9-oxo-, 8,9-anhydro-, 9-epi- and apo-derivatives have been examined. Most of the Cotton effects could be ascribed to the optical anisotropy of the quinoline ring or some more complex chromophore such as the carbonyl group conjugated with the aromatic ring as in the 9-oxo-derivatives. The CD curves of three of these compounds confirmed the Cotton effects at long wavelength resulting from the anisotropy of the aromatic quinoline ring. The mutarotation of the 9-oxo-derivatives has been studied by ORD.

The cinchona alkaloids have been well characterized by structural and stereochemical investigations.[2] The molecules possess four asymmetric carbon atoms in a relatively rigid ring system with a flexible side chain. Knowledge of the configurations[3] of these centers should permit an interesting study of the ORD of these compounds.

Although the chromophore system of the cinchona alkaloids includes only the aromatic quinoline ring for absorption at longer wavelengths, it was hoped that an ORD study would reveal whether or not the quinoline ring would produce anomalous rotatory dispersion curves and permit some hypotheses to be developed as to the relationship of the optical rotatory power to the stereochemistry. Much evidence was obtained as to the nature of the anomalous curves which were shown by these alkaloids and their derivatives, but few conclusions could be developed in answer to the latter question in spite of an optimistic preliminary report to the contrary[1a] since the acyclic model compounds selected for comparison were unsuitable. The evidence of the "optically active" nature of the quinoline ring system either by itself or in conjunction with the hydroxyl or amino function is well supported by the data described below.

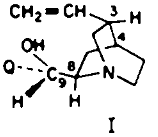
More than 20 cinchona alkaloids and their derivatives were used in this study and included the 9-chloro-9-deoxy-, 9-oxo-, 9-deoxy-, 8,9-anhydro-, and 9-epi-derivatives of quinidine (Ia), quinine (IIa), cinchonine (Ib), and/or cinchonidine (IIb)

[1a] This work was generously supported by the National Institutes of Health, Bethesda, Maryland (GM-07239). A portion of the work described herein has appeared in preliminary form, G. G. Lyle and W. Gaffield, *Tetrahedron Letters* 1371 (1963); 1900 (1964), and was presented before the XIXth meeting of the International Union of Pure and Applied Chemistry, London, July 10–17, 1963; Abstracts A109; [b] Part IV, G. G. Lyle and R. M. Barrera, *J. Org. Chem.* **29**, 3311 (1964); [c] Present address: Western Regional Research Laboratory, Albany, California, 94710.

[2] R. B. Turner and R. B. Woodward in *The Alkaloids* (edited by R. Manske and H. Holmes) Vol. 3, pp. 1–63. Academic Press, New York (1953).

[3a] V. Prelog and E. Zalán, *Helv. Chim. Acta* **27**, 535, 545 (1944); [b] G. G. Lyle and L. Keefer, Abstracts, 149th meeting American Chemical Society, Detroit, Michigan, April 4–9, 1965, p. 59P.

as well as a few compounds of the apoquinine series (III). A comparison of the ORD data for quinidine (Ia) and quinine (IIa) with the anhydro-derivative quinene (IVa) shows that the strong optical rotatory power at the D-line of these alkaloids is due predominantly to the asymmetric carbons (C-8 and C-9) bearing the hydroxyl and amino groups which are also in closest proximity to the aromatic ring. The loss of asymmetric at these positions resulted in a numerical change in the D-line molecular rotations of −613° for quinidine (Ia) and + 659° for quinine (IIa). Loss of asymmetry at C-3 by formation of apo-derivatives III, however, caused a change of only −155° in the D-line molecular rotation (cupreine (IIc) → apocupreine (IIIc).



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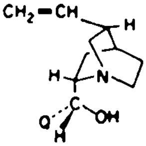

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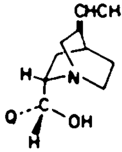

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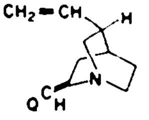

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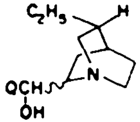

V

a: Q = 6'-methoxy-4'-quinolyl
b: Q = 4'-quinolyl
c Q = 6'-hydroxy-4'-quinolyl
d Q = 6'-β-hydroxyethoxy-4'-quinolyl

The ORD curves of the cinchona alkaloids showed low intensity Cotton effects in the region corresponding to the long wavelength UV absorption bands. The question of the optical anisotropy of an aromatic ring in the vicinity of an asymmetric center which has been discussed by several authors[4] has been answered unequivocally in the specific case of phenyl alanine[4d] on the basis of both experimental and theoretical grounds. Although the phenyl group is responsible for the weak Cotton effects cited in several instances, the quinoline ring has not been subjected to study. The curves of quinine and quinidine (Fig. 1) and the related alkaloids and their derivatives (*vida infra*) showed Cotton effects of moderate amplitude above 250 mμ resulting from absorption bands due to the quinoline ring. Comparison of the ORD, CD and UV curves of quinine (Fig. 1, 2) showed that the Cotton effects centered at 331, 319, 291, and 279 mμ in the ORD corresponded to UV maxima at 332, 322, 290 (sh), and 280 mμ. The shoulders at 269 and 223 mμ and the maximum at 231 mμ were either hidden under the powerful, negative Cotton effect with a trough at 243 mμ (Fig. 1) or out of the instrumental range. The conclusion is inescapable that every UV absorption band in the curve of quinine is optically active. Confirmation of the long wavelength Cotton effects may be seen in the CD curve (Fig. 2) which shows a broad negative maximum at 330–320 mμ and is most likely an overlap of two Cotton effects at 332 and 322 mμ. It is probable

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[4a] G. G. Lyle, *J. Org. Chem.* **25**, 1779 (1960); [b] W. Kuhn and H. Biller, *Z. Physik. Chem.* **B29**, 1 (1935); [c] B. Sjoberg, *Acta Chem. Scand.* **14**, 273 (1960); [d] A. Moscowitz, A. Rosenberg and A. E. Hansen, *J. Amer. Chem. Soc.* **87**, 1813 (1965); [e] L. Verbit, *J. Amer. Chem. Soc.* **87**, 1617 (1965); [f] A. Yogev and Y. Mazur, *Chem. Commun.* 388 (1965).

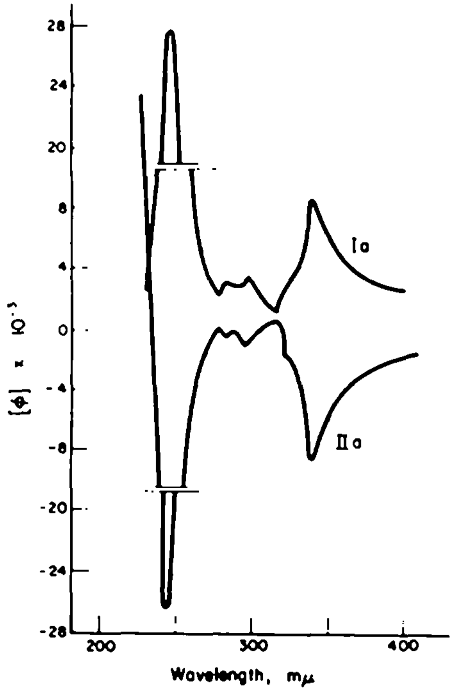

FIG. 1. ORD curves of quinidine (Ia) and quinine (IIa) in methanol.

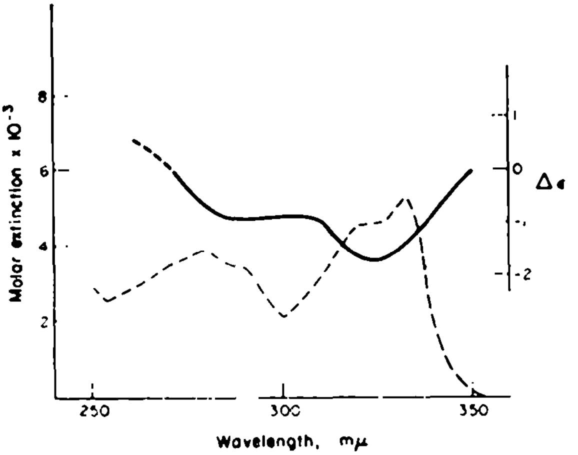

FIG. 2. UV absorption (- - -) and CD (——) curves of quinine (IIa). The dotted portion of the CD curve from 276–270 mμ may be an instrumental artefact.

that these absorption bands result from electronic transitions of the quinoline ring, the longer wavelength band corresponding to the $\pi \rightarrow \pi^*$ transition of the ^1L_b state, but the origin of the 322 mμ absorption is less possible to adduce.[6] In quinoline, the absorption band at 313 mμ has been attributed to the ^1L_b transition and support for this assignment has been obtained by a study of substituted quinolines. A methoxyl

[6] H. H. Jaffe and M. Orchin, *Theory and Applications of Ultraviolet Spectroscopy* pp. 367–369. Wiley, New York (1962).

group at the 6-position causes a bathochromic shift of this band to 325 mμ.[6] Cinchonidine (IIb) which does not possess the 6′-methoxyl group absorbs at 314 mμ.

The shorter wavelength Cotton effect shown in the CD curve of quinine (IIa) is also negative and occurs between 270 and 300 mμ, resulting most likely from the UV absorption band at 280 mμ (ε 3800) in combination with the shoulder at 290 mμ. The 280 mμ band is so close to that of lepidine (4-methylquinoline) in both wavelength (280 mμ) and intensity (ε 4800)[7] that it may be described as a ^1L_a transition and this CD curve provides the first evidence for the optical anisotropy of such an absorption band (analogous to the *K* band of benzene at about 200 mμ). It is even weaker in both the ORD and the CD curves than the long wavelength Cotton effect.

The most intense Cotton effect occurred in almost every case at low wavelength, the estimated midpoint of the curve falling at 230–235 mμ. The UV spectra of the quinine family showed strong absorption at 230–235 mμ while the derivatives of cinchonine (the B series) gave a small hypsochromic shift of this band to 225–229 mμ. Quinoline has similar UV absorption at 225 mμ (log ε 4·54) while 6-methoxyquinoline had a slight displacement of this band to longer wavelength, 227 mμ (log ε 4·56) with a shoulder at 233 mμ (see Experimental). Every cinchona alkaloid and derivative examined gave a strong UV band at 225–235 mμ.

Quinine (IIa) and quinidine (Ia) gave almost exact mirror image curves of their ORD. This supports the assumption[2] that these alkaloids are of enantiomeric stereochemistry at those centers in the alkaloids which control the Cotton effects. These two compounds have identical configurations at C-3 and C-4 but these centers have little effect on the rotatory power except for some positive background rotation which causes the intensities of the extrema of quinine to be less negative than they are positive in quinidine. The fact that the curves for quinine and quinidine are essentially of mirror image appearance indicates the possible diagnostic usefulness of the Cotton effects of relatively large amplitude at long and short wavelengths.

Since the stereochemistry at C-9 and C-8 probably governs the signs of some of the Cotton effects, changes in the stereochemistry should permit a correlation of the Cotton effect with the particular chromophore. Reduction of the isolated double bond of the alkaloids produced derivatives V whose longest wavelength Cotton effects were essentially identical with those of the alkaloids I and II. There was, however, a loss of one Cotton effect or of fine structure in the region 290–280 mμ in the curves of Va, Vb and epihydroquinidine (VIa).

Table 1 lists the midpoints or long wavelength extrema of each Cotton effect and its sign along with the UV absorption data of several of the alkaloids and derivatives. A comparison of the curve of the chloro derivative VIIIa with those of quinidine (Ia) and epihydroquinidine (VIa) shows the similarity of VIIIa with VIa rather than with Ia. This offers support for the idea that in these basic alkaloids replacement of the hydroxyl group by chlorine using thionyl chloride proceeded by inversion of configuration. Both VIa and VIIIa gave strong, negative Cotton effects at low wavelength with troughs at 245 and 246 mμ, respectively, while quinidine (Ia) has an intense peak at a similar point, 244 mμ. This Cotton effect is undoubtedly subject to diverse conformational and solvational effects, but it seems to reflect the

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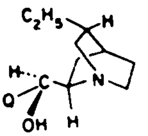
[6] *Organic Electronic Spectral Data* (Edited by H. Ungnade) Vol. II, p. 206. Interscience, New York (1960).

[7] Ref. 6, p. 205.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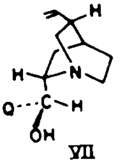
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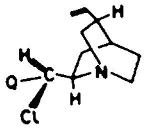
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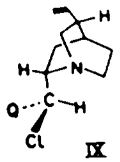
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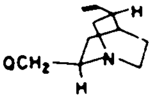
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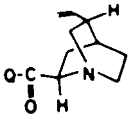
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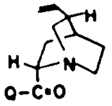
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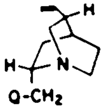
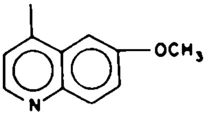
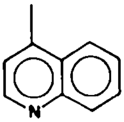

XIII

a: Q =



b: Q =



asymmetry at C-9. It is, of course, impossible to correlate unequivocally the hydroxyl and chloride groups although they apparently are of similar polarizability when they are of the type $\mathrm{Ar}{-}\overset{\diagdown}{\underset{\diagup}{\mathrm{C}}}{-}\mathrm{X}$.[8] Further study of halogenated systems would be of interest.

The ORD data were analysed[4a] using a one-term Drude equation ($[\phi] = A/(\lambda^2 - \lambda_0^2)$) and the dispersion constants (λ_0^2) were found to have little significance. The calculation of the rotation constants was of greater interest and provided a basis for comparing the ORD curves. As has been previously pointed out,[4a] the rotation constant (A) reflects the change in rotation over a considerable portion of the spectrum. The advantage of considering a number of wavelengths (generally in excess of ten) rather than a single point is obvious. The magnitude of the A-values reflects the relative steepness of the ORD curves, usually between 650 and 400 mμ in order to use a section of the curve well outside of the absorption band. Several conclusions may be drawn from the data: (i) the A-values for quinine (IIa) and its

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[8] J. H. Brewster, *Tetrahedron Letters* No. 20, 23 (1959).

Table 1. UV and ORD data for some cinchona alkaloids

	UV maxima mμ	Log ε	Midpoint of Cotton effect	Sign of Cotton effect
Quinidine (Ia)	332	3·73	331	+
	321	3·68	319	+
	289sh		291	+
	280	3·61	279	+
	270sh			
	231	4·58	Peak at 244	+
	223sh			
Epihydroquinidine (VIa)	334	3·70	329	−
	325	3·66		
	292sh			
	282	3·53	287	+
	271sh			
	232	4·55	233	−
9-Chloro-9-deoxyquinidine (VIIIa)	337	3·74	333	+
	296sh			
	285	3·52	290	+
	275sh			
	235	4·49	Trough at 246	−
Quinine (IIa)	332	3·73	332	−
	322	3·68	320	−
	290sh		290	−
	280	3·58	280	−
	269sh			
	231	4·52	Trough at 243	−
	223sh			
Cinchonine (Ib)	315	3·51	311	+
	302	3·61		
	284(broad)	3·72	280	−
	226	4·60	229	+
Deoxycinchonine (Xb)	314	3·49	311	+
	301	3·59	299	+
	283	3·72		
	225	4·60	Possible peak at 230	
Cinchene (IVb)	315sh			
	305	4·04	Obscured peak	
	229	4·58	at 262	+

apo-derivatives (III) are close enough to support their similar stereochemistry; (ii) the difference between the alkaloids having 6′-methoxyl substituents (the A series) and those without (the B series) follows a consistent pattern (quinidine (Ia) − cinchonine (Ib) = +55; quinine (IIa) − cinchonidine (IIb) = −59); (iii) the 9-epi derivatives VI and VII consistently showed values closer to zero than those of the natural alkaloids; and (iv) the 9-chloro compounds VIII and IX gave values of the same order of magnitude as the epi derivatives.

The first three of these conclusions indicate that the *A*-values reflect the stereochemical relationships of this family of alkaloids. It is possible to use the values to predict the shapes and approximate intensities of the long wavelength Cotton effects when certain steric changes are made in this family. The values cannot be transferred

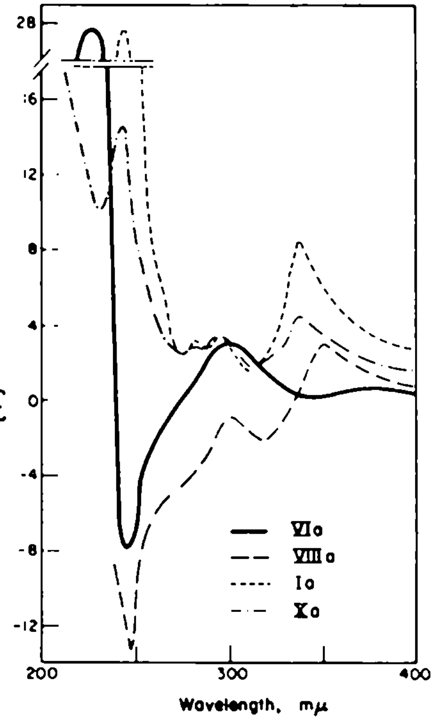

FIG. 3. ORD curves for quinidine (Ia) (– – –), 9-deoxyquinidine (Xa) (– · — · –), 9-chloro-9-deoxyquinidine (VIIIa) (— —), and epihydroquinidine (VIa) (——).

to other families of compounds, however, because they are the result of the total environment and the nature of the aromatic ring causes profound changes in the curves. The fourth conclusion offers further substantiation of the stereochemical assignment of the 9-chloro derivatives VIII and IX. In addition, however, the data show that the intensity of the ORD curve is approximately the same whether a halogen or hydroxyl group is located at the 9-position indicating that factors such as hydrogen bonding probably have little influence on the shapes of the curves of the cinchona alkaloids in the long wavelength region. It is interesting to note the advantages of using the *A*-values as diagnostic tools in the stereochemical assignment rather than attempting to analyse the entire ORD curve. The values for the Drude constants are included in the Experimental. A comparison of the ORD curves of the 9-deoxy-, 9-chloro-9-deoxy-, and 9-epi-derivatives with that of quinidine is shown in Fig. 3.

Although the ORD curves are somewhat confusing in correlating the configurations of the cinchona alkaloids with a particular Cotton effect, the rotation constants *A* indicated the configurations of one group of compounds *relative* to another. These constants, however, were useless for predicting absolute configurations without the proper model systems. One other system of correlation was tried, the molecular rotation difference procedure utilized so successfully in the steroid and terpenoid series.[9] Again, this system requires satisfactory model compounds, and *erythro-* and

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[9] J. A. Mills and W. Klyne in *Progress in Stereochemistry* (Edited by W. Klyne) Vol. I, pp. 209-212. Academic Press, New York, (1954).

TABLE 2. MOLECULAR ROTATION DIFFERENCES (Δ) AT 450 mμ
$\Delta[\phi]_{450} = [\phi]^{a}_{RCHX-CHNR'R''} - [\phi]_{RCH_2CHNR'R''}$

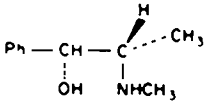
Compound[b]	$[\phi]_{450}$ Base	$[\phi]_{450}$ Salt	$\Delta[\phi]_{450}$ Base	$\Delta[\phi]_{450}$ Salt
Quinine family				
Erythro isomer (IIa)	−1185°	−849°	−385	−60
Threo isomer (VIIa)	+252	+244	+1052	+1033
9-Chloro (IXa)	+204	—	+1004	—
9-Deoxy (XIIIa)	−800	−789	—	—
Ephedrines (XIV)[c]				
Erythro isomer	−3	−117	−46	−178
Threo isomer	+160	+232	+114	+171
Deoxy	+46	+61	—	—

[a] X = Cl or OH

[b] In all compounds the absolute configuration at the carbon bearing the nitrogen atom is the same, i.e. (*S*).

[c] G. G. Lyle, *J. Org. Chem.* 25, 1779 (1960).

threo-2-methylamino-1-phenyl-1-propanol (ephedrine and pseudoephedrine, XIV) gave results that were somewhat equivocal. Although the signs of the molecular rotation differences were consistent, the order of magnitude of the salts and bases was reversed (Table 2). The carbon bearing the amino group in XIV has the absolute configuration of the ephedrines and is the same as that in quinine. It is evident from these results that so little is known of the chromophores operative in the cinchona alkaloids that attempts to establish any rules of correlation of rotation with configuration would be premature.



XIV

The ORD curves of cinchonine (Ib) and deoxycinchonine (Xb) were quite similar with very small Cotton effects in the long wavelength part of the spectrum. The Cotton effect at 311 mμ was almost negligible in deoxycinchonine (a^{10} +0·7) as compared with cinchonine (a +7·9) while the Cotton effect for quinidine (Ia) at 333 mμ, which is probably the result of a similar electronic transition, has an amplitude of +43, more than twice that of deoxyquinidine (Xa, 333 mμ, a +19). It seems that this Cotton effect requires, at least in part, the benzylic type hydroxyl group and the amplitude reflects the chromophoric nature of the aryl group. The positive sign is associated with the configuration possessed by C-9 in quinidine, the negative sign reflecting the mirror image configuration in quinine (IIa) and epihydroquinidine (VIa).

Loss of asymmetry at both C-8 and C-9 as in quinene (IVa) and cinchene (IVb) caused pronounced alternation of the ORD curves. The chromophore present in

[10] The amplitude of a Cotton effect is defined by the expression $([\phi]_{\text{first extremum}} - [\phi]_{\text{second extremum}})/100$ by C. Djerassi and W. Klyne, *J. Chem. Soc.* 4929 (1962).

these styrene-type or diene-amine-type systems is apparently too far away from the asymmetric centers at C-3 and C-4 to produce a major Cotton effect. The absence of a Cotton effect below 250 mμ shows that such an anomaly is associated with asymmetry at C-8 and/or C-9 in the cinchona alkaloids. The sign of the low wavelength Cotton effect appears to be related to the configuration at C-9 rather than C-8, however, since quinine (IIa), 9-chloro-9-deoxyquinidine (VIIIa), and epihydroquinidine (VIa), which have identical configurations at C-3, C-4 and C-9, show negative Cotton effects of apparently large amplitude[10] (VIa, *a* —350), while quinidine (Ia) and cinchonine (Ib) have positive Cotton effects (Ib, *a* +190). The curve for 9-deoxyquinidine (Xa) rises sharply at low wavelength, but the Cotton effect was found to have a much decreased amplitude (237 mμ, *a* +44) as compared with the alkaloids having C-9 asymmetry. It seems that removal of this asymmetric center diminishes the amplitudes of the Cotton effects at long and at short wavelengths (Fig. 3).

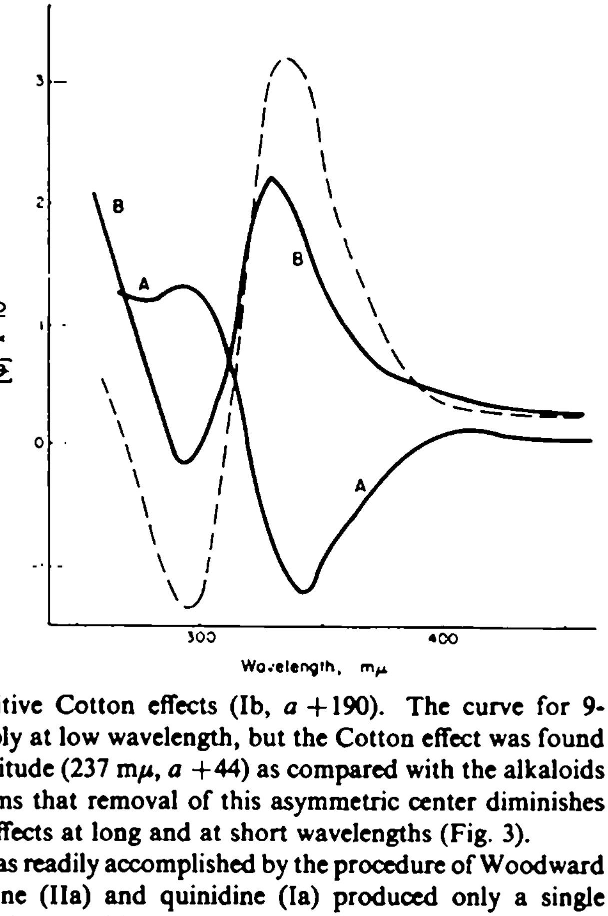


FIG. 4. ORD curves of freshly prepared (curve A) and fully equilibrated (curve B) solutions of cinchonidinone (XIIb). The dashed line (- - -) represents the ORD curve calculated for the unknown cinchoninone (XIb) (see text).

Oxidation of the alkaloids was readily accomplished by the procedure of Woodward and co-workers.[11] Both quinine (IIa) and quinidine (Ia) produced only a single oxo-derivative that was isolated in crystalline form which has been assigned the name quinidinone (implying the stereochemistry of XIa) rather than quininone (XIIa) on the basis of rotation data.[11] The ORD curve of the ketone showed mutarotation undergoing a decrease in its dextrorotation in ethanol. This can best be explained as the result of epimerization of the C-8 center in solution and increase in concentration of the presumably levorotatory quininone (XIIa).

Analogously to the quinidine results, cinchonine (Ib) and cinchonidine (IIb) produced only cinchonidinone (XIIb) after similar oxidation reactions. On standing in ethanol, the ketone underwent rapid mutarotation (Fig. 4), probably producing

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[11] R. B. Woodward, N. L. Wendler and F. J. Brutschy, *J. Amer. Chem. Soc.* 67, 1425 (1945).

an equilibrium mixture of cinchonidinone (XIIb) and the unknown cinchoninone (XIb). The long wavelength, weak Cotton effect in the CD curve shows a change in sign on mutarotation which is obscured in the ORD curve by the strong background rotation. It is possible to calculate an ORD curve for the unknown cinchoninone (XIb) using the data for the pure ketone (XIIb) and the equilibrium mixture (Fig. 4). The calculations indicate that there is about 78% cinchoninone and 22% cinchonidinone in the equilibrium mixture.

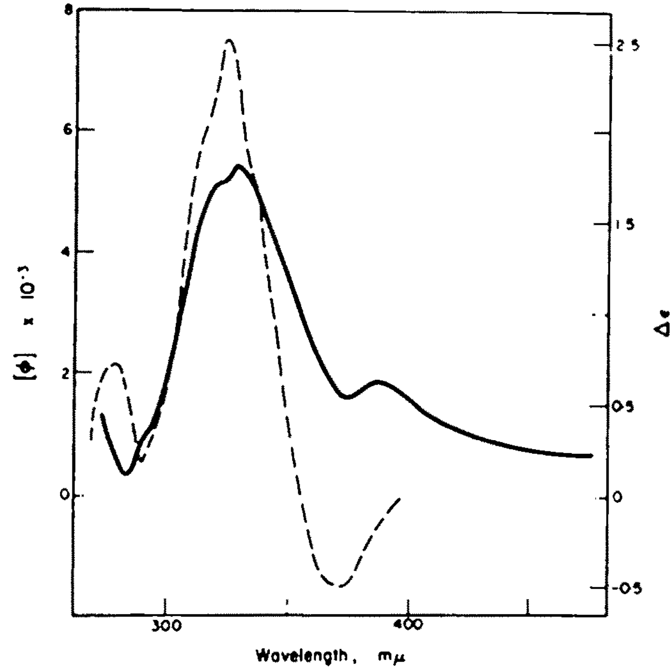

Fig. 5. ORD (——) and CD (- - -) curves of quinidinone (XIa) as freshly prepared solutions.

The CD curve of quinidinone (XIa, Fig. 5) shows a strong, positive Cotton effect at 325 mμ with a shoulder at about 315 mμ. The ORD curve has a double peak at 330 and 320 mμ, whose midpoints agree reasonably well with the CD maxima. Both curves indicate a weak, negative Cotton effect centered at about 365 mμ. It is mathematically possible that the oppositely-signed Cotton effects of the CD curve (and possibly also of the ORD curves) are displaced 10–20 mμ, the strong 325 mμ peak more correctly being located about 340 mμ. A pair of curves can be drawn utilizing these experimental data which would indicate the composite nature of the CD curve which gave a wider separation of the Cotton effects than actually existed. This would be consistent with the UV spectrum which showed maximum absorption for quinidinone in this region at 342 mμ. This type of CD curve has been observed in a number of cyclic ketones where two different species may be present in the solution because of conformational and/or solvational effects, but no decision may be made between effects without variable temperature CD studies.[12] A study of one type of open-chain ketone, the 17-acetylsteroids, has been carried out, and the double-humped CD curves have been attributed to the presence of two conformers whose

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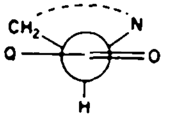
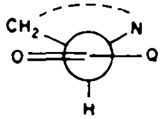
[12] K. M. Wellman, P. H. A. Laur, W. S. Briggs, A. Moscowitz and C. Djerassi, *J. Amer. Chem. Soc.* **87**, 66 (1965).

maximal molecular ellipticities differ by 1–5 mμ.[13] In the cases cited, the CD maxima were relatively symmetrical at 25° but showed apparent increasing population of a single conformer at lower or higher temperature. The CD curve of quinidinone (XIa), however, showed a pronounced difference in the two maxima at room temperature which could indicate a preponderance of one conformer. Low temperature CD studies would clarify this question.

Reduction of quinidinone (XIa) with lithium aluminum hydride gave quinidine (Ia) as the only isolated product. A separation procedure[14] for quinine, quinidine and their 9-epi analogs was carefully followed and essentially none of the other isomers was obtained. In view of a relatively good yield (70%) of quinidine (in contrast to less than 50% in catalytic hydrogenation[11]), the Cram–Prelog rule[15] of asymmetric induction with metal hydrides could have been used to assign the configuration of the C-9 hydroxyl center of quinidine. Because of the certainty at this time that quinidine (Ia) has the *erythro*[3b] configuration of the C-8, C-9 amino alcohol moiety, it is essential to assign a configuration to the ketone in which the quinoline ring is crowded against the quinuclidine bridge and the sequence order of groups is altered according to the "cyclic model" rule of Cram and co-workers.[16] Of the two possible Newman projections of quinidinone having the carbonyl located between the small group, hydrogen, and one of the other groups, XV would be preferred to XVI because of the coordination of the carbonyl and amine with the metal hydride. This conformation would lead to approach of the hydride from the least hindered side, over the hydrogen, and produce the *erythro* isomer quinidine (Ia).



XV



XVI

EXPERIMENTAL[17]

Quinidine (Ia). $[\phi]_{589}$ +710° (*c*, 0·144); *A* +204, λ_0 273; lit.[18] $[\phi]_{589}$ +791° (*c*, 0·7735, alcohol). R. D. (Fig. 1) in methanol (*c*, 0·105): $[\phi]_{400}$ +2560°, $[\phi]_{330}$ +8500°, $[\phi]_{313}$ +1240°, $[\phi]_{300}$ +3550°, $[\phi]_{290}$ +2780°, $[\phi]_{283}$ +3240°, $[\phi]_{276}$ +2320°, $[\phi]_{244}$ +27,800°, $[\phi]_{233}$ +3090°.

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[13] K. M. Wellman and C. Djerassi, *J. Amer. Chem. Soc.* **87**, 60 (1965).

[14] W. E. Doering, G. Cortes and L. H. Knox, *J. Amer. Chem. Soc.* **69**, 1700 (1947).

[15] E. L. Eliel, *Stereochemistry of Carbon Compounds* pp. 68–74. McGraw-Hill, New York (1962).

[16] D. J. Cram and K. R. Kopecky, *J. Amer. Chem. Soc.* **81**, 2748 (1959); D. J. Cram and D. R. Wilson, *ibid.* **85**, 1245 (1963).

[17] ORD curves were obtained with a Rudolph recording spectropolarimeter model 260/658/850/810-609 using 1 cm cells, *t* 25–28°, concentration (g/100 ml) in ethanol except where otherwise stated. Dilution or shortening of the path length was used to permit readings at low wavelength. Some curves were also determined on a Cary 60 instrument at the U.S. Department of Agriculture Western Regional Laboratory, Albany, California with specifications as described by Y. Tomimatsu and W. Gaffield, *Biopolymers* **3**, 509 (1965). UV spectra were obtained on a Cary 14 and D-line rotations on a Franz Schmidt and Haensch polarimeter. The physical constants agreed with literature values as cited. CD curves were obtained in ethanol solution on Jouan Dichrograph instruments. Molecular rotations $[\phi]_\lambda = [\alpha]$M.W./100 are given in the form suggested by C. Djerassi and W. Klyne, *Proc. Chem. Soc.* 55 (1957). Following the D-line rotation or ORD data in the proper solvent are reported the rotation constant *A* and the square root ($\lambda_0 \times 10^4$) of the dispersion constant.

[18] P. Rabe, E. Kuliga, D. Marschall, W. Naumann and W. F. Russell, *Liebig's Ann.* 373, 85 (1910).

Quinidine hydrochloride. R. D. in methanol (*c*, 0·082): $[\phi]_{400}$ +4310°, $[\phi]_{375}$ +7990°, $[\phi]_{325}$ −2330°(broad), $[\phi]_{300}$ +712°(sh), $[\phi]_{260}$ +17,000°, $[\phi]_{247}$ −16,200°, $[\phi]_{233}$ −8900°(sh), $[\phi]_{220}$ +7120°.

Cinchonine (Ib). $[\phi]_{589}$ +793° (*c*, 0·0520); *A* +149, λ_c 280; lit.[18] $[\phi]_{589}$ +661° (*c*, 0·606, alcohol). R. D. in methanol (*c*, 0·037): $[\phi]_{400}$ +1740°, $[\phi]_{314}$ +5140°, $[\phi]_{310}$ +4350°, $[\phi]_{305}$ +4740°, $[\phi]_{290}$ +4350°(sh), $[\phi]_{283}$ +3560°, $[\phi]_{278}$ +4740°, $[\phi]_{276}$ +4540°, $[\phi]_{234}$ +29,200°, $[\phi]_{224}$ +9880°, $[\phi]_{220}$ +13,000°.

Hydroquinidine (Va, C-8 *R*[19]). R. D. in 95% ethanol (*c*, 0·202): $[\phi]_{589}$ +745°, $[\phi]_{335}$ +7620°, $[\phi]_{315}$ +650°, $[\phi]_{300}$ +3230°, $[\phi]_{270}$ +1780°, $[\phi]_{265}$ +4210°. Lit.[20a] $[\phi]_{589}$ +753° (*c*, 2·02, alcohol).

Quinine (IIa). $[\phi]_{589}$ −562° (*c*, 0·416); *A* −159, λ_c 260; lit.[18] $[\phi]_{589}$ −512° (*c*, 2·136, alcohol). R. D. (Fig. 1) in methanol (*c*, 0·095): $[\phi]_{400}$ −1950°, $[\phi]_{336}$ −8710°, $[\phi]_{315}$ +512°, $[\phi]_{296}$ −1020°, $[\phi]_{287}$ −171°, $[\phi]_{283}$ −512°, $[\phi]_{277}$ +171°, $[\phi]_{243}$ −26,500°, $[\phi]_{233}$ +15,400°.

C. D. (Fig. 2) (*c*, 0·003443): $\Delta\varepsilon_{360}$ 0, $\Delta\varepsilon_{335-330}$ −1·8, $\Delta\varepsilon_{300-285}$ −0·9, $\Delta\varepsilon_{276}$ 0, $\Delta\varepsilon_{270}$ +0·45.

Quinine hydrochloride. R. D. (*c*, 0·068): $[\phi]_{650}$ −478°, $[\phi]_{589}$ −478°, $[\phi]_{375}$ −3980°, $[\phi]_{350}$ −2020°.

Cinchonidine (IIb). R. D. (*c*, 0·124): $[\phi]_{650}$ −95°, $[\phi]_{589}$ −119°, $[\phi]_{315}$ −1830°, $[\phi]_{300}$ −309°, $[\phi]_{275}$ −522°, *A* −100, λ_c 234. Lit.[18] $[\phi]_{589}$ −266° (*c*, 0·878, alcohol). R. D. in methanol (*c*, 0·192): $[\phi]_{600}$ −320°, $[\phi]_{589}$ −335°, $[\phi]_{340-330}$ ~ −1950°(sh), $[\phi]_{314}$ −3650°, $[\phi]_{310}$ −2970°, $[\phi]_{305}$ −3350°, $[\phi]_{302}$ −2510°, $[\phi]_{285}$ −1600°, $[\phi]_{255}$ −8450°(sh), $[\phi]_{233}$ −38,500°, $[\phi]_{220}$ +22,100°(sh), $[\phi]_{210}$ +44,200°.

Cupreine (IIc). R. D. (*c*, 0·335): $[\phi]_{700}$ −306°, $[\phi]_{589}$ −436°; (*c*, 0·070): $[\phi]_{345}$ −3060°, $[\phi]_{330}$ −1460°, $[\phi]_{325}$ −1510°, *A* −117, λ_c 300. Lit.[20b] $[\phi]_{589}$ −546° (MeOH).

Apocupreine (IIIc). R. D. (*c*, 0·084): $[\phi]_{650}$ −517°, $[\phi]_{589}$ −591°, $[\phi]_{345}$ −3840°, $[\phi]_{310}$ −2590°, *A* −176, λ_c 274. Lit.[20c] $[\phi]_{589}$ −667° (alcohol).

6′-(β-Hydroxyethyl)-apocupreine (IIId). Dihydrochloride. R. D. (*c*, 0·345): $[\phi]_{650}$ −433°, $[\phi]_{589}$ −658°, $[\phi]_{365}$ −3760°, $[\phi]_{350}$ −2210°, *A* −162, λ_c 311. Lit.[21] $[\phi]_{589}$ −974° (*c*, 1, water).

Hydroquinine (Va, C-8 *S*[19]). R. D. (*c*, 0·101): $[\phi]_{589}$ −450°, $[\phi]_{334}$ −11,000°, $[\phi]_{312}$ −1300°, $[\phi]_{303}$ −5000°, $[\phi]_{276}$ −1300°, $[\phi]_{265}$ −4000°. Lit.[22] $[\phi]_{589}$ −463° (*c*, 1, alcohol).

Epihydroquinidine (VIa). $[\phi]_{589}$ +261° (*c*, 1·265); *A* +87, λ_c 130. Lit.[23] $[\phi]_{589}$ +230° (alcohol). R. D. (Fig. 3) in methanol (*c*, 0·075): $[\phi]_{400}$ +435°, $[\phi]_{367}$ +520°, $[\phi]_{334}$ +350°, $[\phi]_{307}$ +3050°, $[\phi]_{276}$ −80°(sh), $[\phi]_{245}$ −7830°, $[\phi]_{225-221}$ +27,000°, $[\phi]_{215}$ +22,600°.

Epiquinidine monothiocyanate. R. D. in water (*c*, 0·25): $[\phi]_{650}$ +238°, $[\phi]_{589}$ +249°, $[\phi]_{365}$ +1260°, $[\phi]_{350}$ +611°; *A* +80, λ_c 247. Lit.[24] $[\phi]_{589}$ +144° (*c*, 0·4496, water).

Epiquinine (VIIa). R. D. (*c*, 0·838): $[\phi]_{650}$ +116°, $[\phi]_{589}$ +124°, $[\phi]_{365}$ +441°, *A* +36, λ_c 247. Lit.[25] $[\phi]_{589}$ +139°, (*c*, 0·95, alcohol).

Epiquinine dihydrochloride. R. D. (*c*, 1·026): $[\phi]_{650}$ +128°, $[\phi]_{589}$ +155°, $[\phi]_{425-410}$ +256°, $[\phi]_{380}$ +159°, *A* +56, λ_c 106. Lit.[26] $[\phi]_{589}$ +131° (*c*, 0·8, alcohol).

Quinene (IVa) *dihydrochloride hydrate.* R. D. in water (*c*, 0·780): $[\phi]_{650}$ +81·5°, $[\phi]_{589}$ +92·5°, $[\phi]_{450}$ +158°, *A* +43, λ_c 332. Lit.[26] $[\phi]_{589}$ +69·7° (*c*, 1·060, water) for anhydrous salt.

Cinchene (IVb). $[\phi]_{589}$ +142° (*c*, 0·136), *A* +120, λ_c 288. R. D. in methanol (*c*, 0·048): $[\phi]_{400}$ +547°, $[\phi]_{300}$ +3050°(broad), $[\phi]_{285}$ +2930°, $[\phi]_{263}$ +5470°, $[\phi]_{240}$ +3050°, M.p. 122–124°; lit.[27] m.p. 123–125°; no rotation given.

9-Chloro-9-deoxyquinidine (VIIIa). $[\phi]_{589}$ +212° (*c*, 0·5); *A* +49, λ_c 337; lit.[18] $[\phi]_{589}$ +121° (*c*, 1·943, alcohol). R. D. (Fig. 3) in methanol (*c*, 0·073): $[\phi]_{400}$ +704°, $[\phi]_{330}$ +3050°, $[\phi]_{317}$ −2110°, $[\phi]_{300}$ −822°, $[\phi]_{270}$ −5000°(sh), $[\phi]_{240}$ −13,300°, $[\phi]_{240}$ −8570°.

9-Chloro-9-deoxyquinine (IXa). $[\phi]_{589}$ +160° (*c*, 0·5), *A* +62, λ_c 231; lit.[18] $[\phi]_{589}$ +209° (*c*, 1·966, alcohol). R. D. in methanol (*c*, 0·042): $[\phi]_{650}$ +204°, $[\phi]_{450}$ +220°, $[\phi]_{390}$ 0°, $[\phi]_{353}$ −1880°, $[\phi]_{341}$ 0° $[\phi]_{330-315}$ +3590°, $[\phi]_{310}$ +3350°, $[\phi]_{275}$ +4730°(sh), $[\phi]_{250}$ +15,400°, $[\phi]_{215-213}$ −21,800°, $[\phi]_{205}$ −7840°

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[19] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).

[20a] *The Merck Index* (Edited by P. G. Stecher) p. 537, 7th ed. Merck & Co., Inc., Rahway, N.J. (1960). [b] p. 299. [c] p. 95.

[21] C. L. Butler and A. G. Renfrew, *J. Amer. Chem. Soc.* **60**, 1473 (1938).

[22] *The Merck Index* (Edited by P. G. Stecher) p. 537, 7th ed. Merck & Co., Inc., Rahway, N.J. (1960).

[23] L. Prajer and J. Suszko, *Roczniki Chem.* **26**, 531 (1952); *Chem. Abstr.* **49**, 2448 (1955).

[24] P. Rabe and H. Höter, *J. prakt. Chem.* **154**, 66 (1939); *Chem. Abstr.* **34**, 1671 (1940).

[25] *The Merck Index* (Edited by P. G. Stecher) p. 406, 7th ed. Merck & Co., Inc., Rahway, N.J. (1960).

[26] M. Heidelberger and W. A. Jacobs, *J. Amer. Chem. Soc.* **42**, 1489 (1920).

[27] W. J. Comstock and W. Koenigs, *Ber. Dtsch. Chem. Ges.* **17**, 1984 (1884).

9-*Chloro-9-deoxycinchonine* (VIIIb) *hydrochloride*. R. D. in 50% ethanol–water (*c*, 0·356): $[\phi]_{650}$ +118°, $[\phi]_{589}$ +160°, $[\phi]_{335}$ +1340°, $[\phi]_{285}$ +343°, A +50, λ_c 215. Lit.[10] $[\phi]_{589}$ +173°, (1·5555, water).

9-*Deoxyquinidine* (Xa) *dihydrate*. $[\phi]_{589}$ +550° (*c*, 0·5); A +174, λ_c 207; lit.[10] $[\phi]_{589}$ +592° (*c*, 2·254, alcohol). R. D. (Fig. 3) in methanol (*c*, 0·050): $[\phi]_{400}$ +1550°, $[\phi]_{337}$ +4610°, $[\phi]_{325}$ +2620° (sh), $[\phi]_{315}$ +1790°, $[\phi]_{306}$ +3310°, $[\phi]_{297}$ +2620°, $[\phi]_{291}$ +2890°, $[\phi]_{278}$ +2410°, $[\phi]_{243}$ +14,600°, $[\phi]_{233}$ +10,200°, $[\phi]_{215}$ +18,700°.

9-*Deoxyquinine* (XIIIa). R. D. (*c*, 0·434): $[\phi]_{650}$ −227°, $[\phi]_{589}$ −263°, $[\phi]_{335}$ −1780°, $[\phi]_{365}$ −1240°, A −101, λ_c 189. Lit.[10] $[\phi]_{589}$ −302° (*c*, 2·021, alcohol).

9-*Deoxyquinine hydrochloride*. R. D. (*c*, 0·485): $[\phi]_{650}$ −363°, $[\phi]_{589}$ −427°, $[\phi]_{300}$ −1600°.

9-*Deoxycinchonine* (Xb). $[\phi]_{589}$ +612° (*c*, 0·10); lit.[10] $[\phi]_{589}$ +503° (*c*, 1·965, alcohol). R. D. in methanol (*c*, 0·019): $[\phi]_{400}$ +1170°, $[\phi]_{318}$ +2950°, $[\phi]_{310}$ +2880°, $[\phi]_{300}$ +3100°, $[\phi]_{297}$ +2950°, $[\phi]_{293-290}$ +3100°, $[\phi]_{285}$ +2950°, $[\phi]_{231}$ +25,100°, $[\phi]_{227}$ +24,400°, A +229, λ_c 152.

Quinidinone (XIa). R. D. (Fig. 5) in ethanol (*c*, 0·24, 0·07, 0·01): $[\phi]_{650}$ +443°, $[\phi]_{589}$ +460°, $[\phi]_{400}$ +1100°, $[\phi]_{360}$ −46°, $[\phi]_{330}$ +5480°, $[\phi]_{320}$ +5160°(sh), $[\phi]_{285}$ +322°, $[\phi]_{275}$ +1290°, A +109, λ_c 266. These curves were completely measured within 15 min of preparation of the sample solutions. Lit.[14] $[\phi]_{589}$ +386° (*c*, 0·1088, rotation measured 15 min after solution was prepared). R. D. after 18 hr in ethanol (*c*, 0·125): $[\phi]_{650}$ +77·3°, $[\phi]_{589}$ +283°, $[\phi]_{500}$ +232°, $[\phi]_{400}$ +644°, $[\phi]_{385}$ +77·3°, A +42, λ_c 333. Lit.[14] $[\phi]_{589}$ +238° (rotation of above solution after standing for 16 hr).

C. D. (*c*, 0·1086): $\Delta\varepsilon_{396}$ 0, $\Delta\varepsilon_{373}$ −0·473, $\Delta\varepsilon_{350}$ 0, $\Delta\varepsilon_{335}$ +2·45, $\Delta\varepsilon_{315}$ +1·84(sh), $\Delta\varepsilon_{300}$ +0·177, $\Delta\varepsilon_{290}$ +0·728, $\Delta\varepsilon_{270}$ +0·290.

Reduction of Quinidinone (XIa). A suspension of 0·5 g LAH in anhydrous ether was stirred for 15 min and 1·6 g quinidinone (XIa) was added in small portions. The mixture was heated under reflux for 0·5 hr. The reaction mixture was decomposed with water followed by 40% NaOH and extracted with ether. After the ether extracts were dried and concentrated, 1·22 g material, m.p. 130–145°, was obtained which gave hydroxyl but no carbonyl absorption in the IR. The ORD curve indicated that the product was not pure quinidine, but evidence that it consisted chiefly of quinidine (Ia) was obtained by carrying out the separation scheme of Doering, Cortes and Knox.[14] From the material obtained above, 1·20 g quinidine acid tartrate, m.p. 108–132° (dec.), lit.[14] m.p. 110–125° (dec.), was isolated which indicated that quinidinone was converted to quinidine in at least 72% yield. No epiquinine or epiquinidine was obtained in the form of the neutral dibenzoyl-*d*-tartrates in the separation procedure. About 12% of residual alkaloids was recovered which formed no crystalline derivatives during the separation procedure.

Cinchonidinone (XIIb). $[\phi]_{589}$ ±0° (10 min after compound was dissolved), A +13, λ_c 299, +61° (22 min), +100° (32 min), +130° (43 min) (*c*, 0·47); +280° (after one week, *c*, 0·125); A +111, λ_c 281; lit.[28] $[\phi]_{589}$ +9·6° (*c*, 1·216, after 10 min), +219° (after 20 hr). R. D. (Fig. 4) in methanol (*c*, 0·013, 0·016): $[\phi]_{375}$ −360°, $[\phi]_{342-340}$ −1240°, $[\phi]_{305-300}$ +1260°, $[\phi]_{270}$ +1170°, $[\phi]_{265}$ +1260° (all readings were taken no more than 2 min after dissolution). R. D. in methanol (*c*, 0·12: $[\phi]_{375}$ +731°, $[\phi]_{330-327}$ +2360°, $[\phi]_{300}$ −146°, $[\phi]_{265}$ +2120° (after mutarotation ceased).

C. D. (*c*, 0·1415, 0·1680): $\Delta\varepsilon_{444}$ 0, $\Delta\varepsilon_{370}$ +0·189, $\Delta\varepsilon_{355}$ +0·085 (immediately on dissolution): $\Delta\varepsilon_{430}$ 0, $\Delta\varepsilon_{415}$ −0·011(sh), $\Delta\varepsilon_{347}$ −0·059, $\Delta\varepsilon_{355}$ −0·053 (after 2 hr).

6-*Methoxyquinoline*. B.p. 150–152° at 10 mm; lit.[29] b.p. 153° at 12 mm. $\lambda_{\max}^{\mathrm{EtOH}}$ (log ε): 330 mμ (3·71), 318 (3·70), 276 (3·55), 268 (3·54), 233 (sh), 227 (4·56), 212 (4·52).

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[28] A. G. Renfrew and L. H. Cretcher, *J. Amer. Chem. Soc.* **57**, 738 (1935).

[29] E. Maschmann, *Ber. Dtsch. Chem. Ges.* **59**, 2825 (1926).