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ROTATORY DISPERSION STUDIES III. THE CINCHONA ALKALOIDS (1,2)

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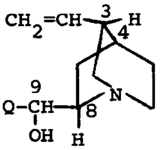
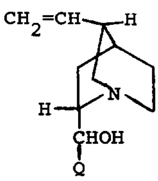
The absolute configurations of the asymmetric centers at C-3, C-4 and C-8 of the cinchona alkaloids (I,II) have been firmly established by a series of investigations (3). The configuration of the C-9 hydroxyl group which is outside of the quinuclidine ring has remained in some question.

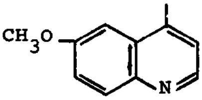
Prelog and Hafliger (4) compared the basicities of the alkaloids and their C-9 epi-bases with the similarly epimeric ephedrine and pseudoephedrine (III) concluding that the natural alkaloids being more basic than their C-9 epimers had the same relative configuration at C-8 and C-9 as ephedrine (i.e., erythro or "mesoid") while the epi-bases possessed the same stereochemistry as pseudoephedrine (i.e., threo or "transoid"). Doering, Cortes and Knox postulated a similar conclusion based on the reduction of the C-9 ketones (5).



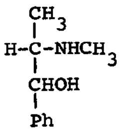
I



II

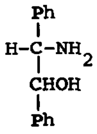
Q = 

Although the evidence for the assignment of the C-9 configuration seemed reasonable, it is not conclusive and a study of the optical rotatory dispersion of the cinchona alkaloids was undertaken. The ORD curves of the natural products and some of the 9-epi-, 9-deoxy-, and 9-oxo-derivatives are summarized in Table I. The maximum rotation is recorded and probably represents the first extremum of a Cotton effect curve except in the case of quinene. The existence of the Cotton effect in all cases appeared to be real (6) and not the result of light scattering as has been suggested (7) when the chromophore involved an aromatic ring. There was no significant change in the curves on dilution, and the model compounds (IV) were examined as their racemates and showed no deviation from zero rotation in the region 695 to 230 mμ. Essentially enantiomeric isomers such as quinine and quinidine gave approximately mirror image curves. Although the entire Cotton effect could not be measured, the location and intensity of the first extremum are a reasonable indication of the sign and position of the Cotton effect. The wavelengths of the first extrema are 20-30 mμ longer than the ultraviolet absorption band at longest wavelength except in the case of quinidinone ($\lambda_{max.}$ 343 mμ). For steroidal ketones, the difference between the wavelengths of the first extrema and ultraviolet absorption maxima is generally 20-30 mμ (8). The difference is larger in some cases, e.g. 2α-iodo-5α-cholestan-3-one, 57 mμ (9).



$$\begin{array}{c} CH_3 \\ | \\ H-C-NHCH_3 \\ | \\ CHOH \\ | \\ Ph \end{array}$$

III



$$\begin{array}{c} Ph \\ | \\ H-C-NH_2 \\ | \\ CHOH \\ | \\ Ph \end{array}$$

IV

Although a single term Drude equation cannot describe the Cotton effect of an ORD curve, the equation was applied to the long wavelength portion of the curves which is outside of the region of absorption. The slope of the straight line obtained from a plot of the square of the wavelength against the reciprocal of the molecular rotation as abscissa is designated A and was calculated in practice from a least squares solution of the equation by means of an IBM-1620 computer (10). The A-values are given in Table I.

All of the alkaloids and their derivatives having the same relative configurations at C-8 and C-9 as quinidine (I) and quinine (II) showed curves of large intensity as compared with those of the 9-epi series. The A-values of the two groups were of considerably different numerical magnitude with the normal series having the larger values. A similar pattern has been noted in the case of the ephedrines (III) (10) and 2-amino-1,2-diphenylethanols (IV) (11). In these cases the absolute configurations of all asymmetric centers have been unequivocally established and the intensity of the curves and magnitude of the A-values are much larger for the threo isomers than for the epimeric erythro isomers. The difference in these optical rotation characteristics in the case of the compounds of known configuration (III and IV) thus permits the application of the results to the cinchona alkaloids. Since quinine and quinidine have much larger A-values and produce curves of greater intensity than the corresponding C-9 epimers, it is probable that the relative configuration at C-8 and C-9 of the natural products is threo and of the C-9 epimers erythro.

Oxidation of either quinine or quinidine produces a single ketone, quinidinone, whose optical rotatory dispersion curve undergoes a decrease with time in its positive Cotton effect (see Table I). Since the absolute configuration of quinidinone is known, the application of the Octant Rule (12) to the ORD curve indicates that the preferred conformation of quinidinone is that pictured in Va rather than Vb, the former being consistent with a positive Cotton effect while the latter would show a negative Cotton effect. The catalytic hydrogenation of Va would be expected to produce a threo product. The earlier assignment of the erythro configuration to quinidine from the hydrogenation experimental data (5) was based on the assumption of the Vb conformation for quinidinone. When quinidinone was reduced with lithium aluminum hydride, a 76% yield of mixed alkaloids was obtained of which 72% was pure quinidine. The remainder of the material was an oily mixture which was not further characterized. This suggests that the reduction with lithium aluminum hydride proceeds by steric approach control which is consistent with the reductive mechanism for sterically hindered ketones. The fact that catalytic hydrogenation and metal hydride reduction of dihydroquinidinone and quinidinone give predominantly dihydroquinidine and quinidine respectively is consistent with the threo configuration of these compounds.

The interpretation of optical rotatory dispersion data is limited by the present scarcity of satisfactory model compounds in this area and by an incomplete theoretical understanding of the effects of the many variables on the RD curves. That the previous assignment of relative configuration of the cinchona alkaloids was in error seems highly probable on the basis of the available ORD information, but additional con-

TABLE I

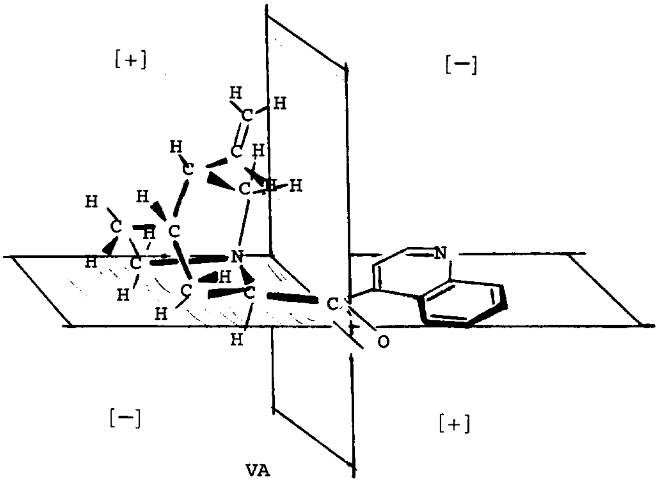
Optical Rotatory Dispersion Data

Compound	[ϕ]	Wavelength in mμ of Maximum Rotation	A-Values
Quinidine (I)	+4520°	350	+204
Quinine (II)	-4130	360	-159
Dihydroepiquinidine	+800	355	+87
Epiquinidine mono-thiocyanate	+1260	365	+80
Quinidinone	+1210	400	+109
Quinidinone (after muta-rotation complete)	+644	400	+42
Deoxyquinidine dihydrate	+2860	360	+168
Quinene dihydrochloride monohydrate	+158	425	+43

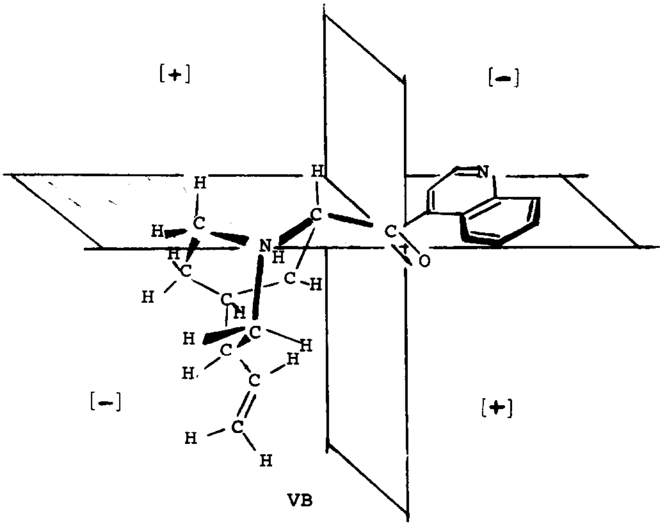
All solutions were measured in a 1 cm. cell in ethanol solution, 27-30°, with concentrations of 0.1 to 1.0 g/100 ml. All compounds agreed in melting point and specific rotation at 589 mμ with those described in the literature. The leading reference to the compounds is the review article by R. Turner and R. Woodward in "The Alkaloids," ed. R. Manske and H. Holmes, Vol. 3, Academic Press, New York, 1953.

firmatory evidence would be desirable. Further work is in progress to this end.

We are grateful to Dr. Alice Renfrew of the Mellon Institute for samples of some of the compounds in this study. The ORD data were obtained on a Rudolph recording spectropolarimeter model 260/655/850/810-614.



VA



VB

Two possible conformations of quinidinone oriented on Octant Rule coordinate system.

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(2) Supported in part by grants from Smith Kline and French Foundation and from National Institutes of Health, GM-07239.

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