Circular Dichroism of Indole Alkaloids. Part 1.[1] Vincane Derivatives

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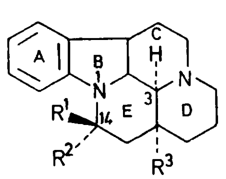
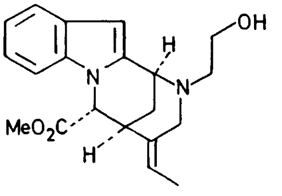
Of the seven c.d. bands found between 320 and 180 nm in vincane derivatives the two at longest wavelengths (^1L_b and ^1L_a transitions) depend mainly on the chirality of rings C and E (*i.e.* the configuration at C-3). The increment of a 14-substituent (3α-compounds: negative for the ^1L_b and positive for the ^1L_a c.d. band) is independent of the nature and stereochemistry of the substituent. 14α-Substituents contribute positively at *ca.* 230 nm to the c.d. of 3α-vincane derivatives, 14β-substituents negatively; at *ca.* 250 nm, however, both give positive contributions. The c.d. increments of individual groups at C-14 over the whole wavelength range (in acetonitrile solution) are additive even for 14-*gem*-disubstituted products. Because of the complex nature of the c.d. between 250 and 200 nm the stereochemistry at C-14 of 3α-vincane derivatives can be deduced only by comparison of their c.d. curves with ' synthetic ' ones.

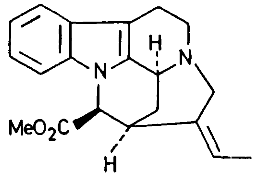
INDOLE shows π ⟶ π* absorption bands at 287, 267, 215, and 196 nm [2-4] which are assigned by comparison with naphthalene spectra [5-7] as α- (^1L_b-), *p*- (^1L_a-), β- (^1B_b-), and β′- (^1B_a-) bands, respectively. They are shifted towards longer wavelengths by substitution.[3,8,9] For optically active indole derivatives Cotton effects have been recorded, and some empirical correlations with absolute configuration have been published (*cf. e.g.* refs. 10—28). Recently Danieli *et al.*[29] described the c.d. of vincamine (6) and its 3- and/or 14-epimers and proposed that the Cotton effect at *ca.* 235 nm can be used to determine the stereochemistry at C-14 of 14-disubstituted derivatives. We have investigated the c.d. spectra of 3α-vincane (1) and several of its 14-mono- and di-substituted products in the range from 330 to 180 nm, and studied in more detail the contribution of a 14-OH or/and 14-CO_2Me group to the different Cotton effects.



(1) $R^1 = R^2 = H, R^3 = Et$
(2) $R^1 = H, R^2 = OH, R^3 = Et$
(3) $R^1 = OH, R^2 = H, R^3 = Et$
(4) $R^1 = H, R^2 = CO_2Me, R^3 = Et$
(5) $R^1 = CO_2Me, R^2 = H, R^3 = Et$
(6) $R^1 = OH, R^2 = CO_2Me, R^3 = Et$
(7) $R^1 = OH$ $R^2 = CH_2OH$ $R^3 = Et$
(8) $R^1, R^2 = O, R^3 = H$
(9) $R^1, R^2 = O, R^3 = Et$



(10)



(11)

C.D. Spectra.—Up to seven c.d. bands can be observed for the vincane derivatives, and bands are numbered from long to short wavelength (Figure 1, I—VII). Bands I and II coincide approximately with the corresponding u.v. maxima (α- and *p*-bands); their positive signs are in general correlated with 3α*H*-stereochemistry.[11,17,20] According to our general interpretation of c.d. bands [16] the signs of the Cotton effects of chiral indole derivatives without the ring E of the vicane system (*e.g.* yohimbanes) are mainly determined by the helicity of ring C (the second sphere of these molecules [16]). The vincane skeleton contains, however, two chiral second spheres (rings C and E), which are approximate enantiomorphs of each other (*cf.* Figure 2). From the known [30] absolute configuration of vincane (1) and the relatively strong positive c.d. of bands I and II we can conclude that the helicity of ring E shown in Figure 2 also leads to a positive Cotton effect in spite of the ' geometrical compensation ' of both the second spheres. Only one simple analogous optically active indole alkaloid is known to us which lacks ring C and whose c.d. has been reported, *viz.* vinoxine (10). Its absolute configuration has, however, only been determined [31] by comparing its c.d. with that of pleiocarpanine (11), where again two chiral second spheres are present, so it cannot be used as a reference compound.

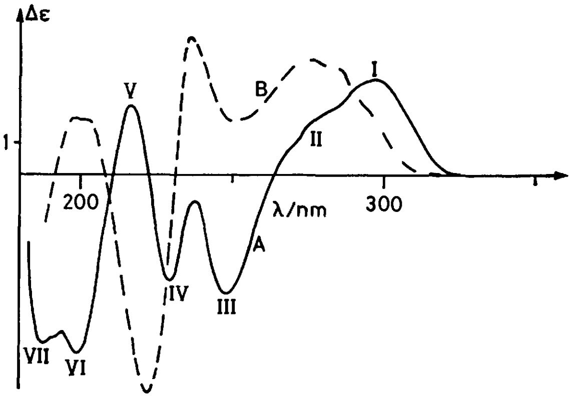


FIGURE 1 C.d. spectra of A, vincane (1) and B, vincamine (6) in acetonitrile solution

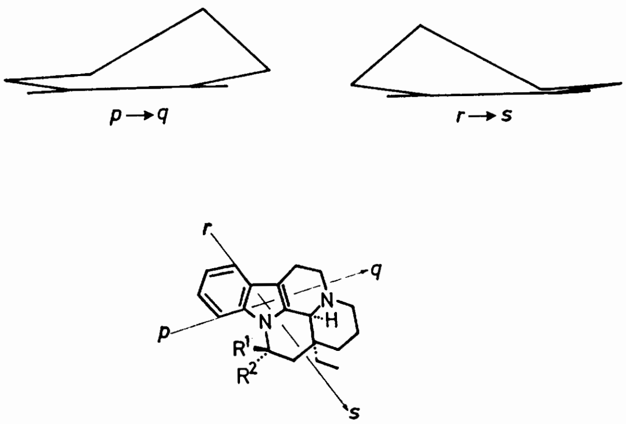


FIGURE 2 Chirality of the second spheres: left, chiral ring C (projection from *p* towards *q*); right, chiral ring E (projection from *r* towards *s*). Computer drawing with co-ordinates from ref. 30.

The c.d. bands III and IV have no strong counterpart in the u.v. spectrum, and two of the other three bands V—VII correspond to the β and β′ bands. By analogy with the c.d. spectra of chiral benzene derivatives [16,32,33] we expect that substitution next to the chromophore should not change the sign of the Cotton effect of band I, but may give larger contributions to the c.d. bands at shorter wavelengths. This is indeed the case and Figure 3 shows difference c.d. spectra obtained by subtracting the c.d. spectrum of vincane (1) from those of the four 14-monosubstituted products (2)—(5). All substituents give a moderate negative contribution to the Cotton effect in band I and two positive ones for the c.d. bands II and III, irrespective of their nature and configuration. We ascribe this effect to changes of polarizability within ring E; a change of conformation within the vincane skeleton * seems improbable because the steric effect of the α- and β-groups work in opposite directions.

A very strong contribution to the Cotton effect of band IV is found at *ca.* 230 nm; it is positive for the two 14α-substitution products (2) and (4) and negative for the 14β-epimers (3) and (5). No such simple correlations with stereochemistry are found for c.d. bands V—VII.

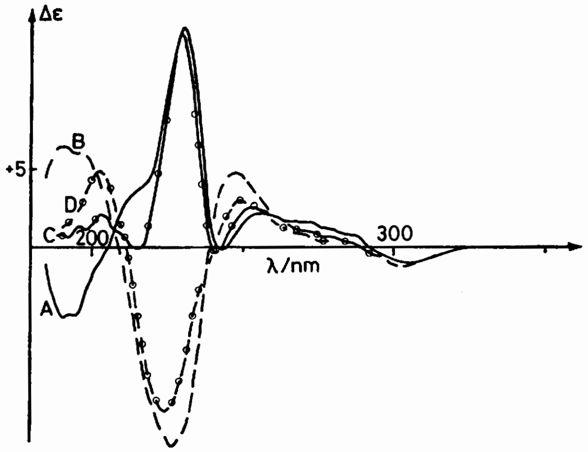


FIGURE 3 Third-sphere contributions to the c.d. of vincane derivatives (difference c.d. spectra): A, Δε(2)—Δε(1); B, Δε(3)—Δε(1); C, Δε(4)—Δε(1); D, Δε(5)—Δε(1)

Additivity of C.D. Contributions.—Although changes of the conformation of 14-substituents due to internal hydrogen bridging and steric interaction by geminal groups cannot be excluded, the c.d. contributions of the third sphere are remarkably additive. We tested this by comparing the sum of the individual contributions of 14β-OH [Δε(3) — Δε(1)] and 14α-CO_2Me [Δε(4) — Δε(1)] with the combined contributions of these two groups in vincamine (6) [Δε(6) — Δε(1)] (Figure 4) and found that for bands I—VI the position, sign, and even the magnitude of the c.d. in the two curves are very similar. Third-sphere contributions are thus additive in this series of indole alkaloids and must, therefore, follow a sector rule.

Since band overlap may lead to appreciable shifts of the real maxima, especially in case of adjacent Cotton effects of opposite sign (*cf.* Table), the determination of the stereochemistry of vincane derivatives by comparison of measured c.d. curves with the 'synthetic' ones obtained from the difference curves of Figure 4 seems to be much more reliable than the use of the sign of one individual Cotton effect alone.

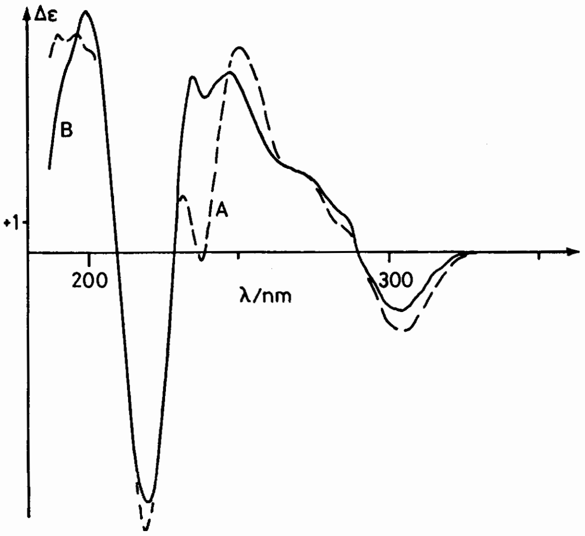


FIGURE 4 Combined third-sphere contributions of 14β-OH and 14α-CO_2Me to the c.d. of vincane derivatives: A, Δε(3) + Δε(4) — 2 × Δε(1); B, Δε(6) — Δε(1)

Vincamone (9) *and Vincaminol* (7).—The c.d. of 20,21-dinorvincamone (8) at wavelengths longer than 240 nm has already been described.[34] Because of the 14-oxo-group the chromophoric system has, however, changed. Thus the c.d. of (8) and of vincamone (9) cannot be directly compared with those of the other vincane derivatives. In the Table we include, however, the c.d. data of (9) for comparison. The c.d. spectrum of vincaminol (7) shows no peculiarities in the short wavelength range.

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* This possibility was suggested by a referee.

Compound	C.d. bands $\lambda_{max.}$/nm ($\Delta\varepsilon$) [a] I	II	III	IV	V	VI	VII
(1)	297 (+3.20)	280 (+2.10)	248 (−3.91)	229 (−3.51)	216 (+2.32)	199 (−6.0)	187 (−5.6)
(2)	287 (+3.22)	274 (+3.00)	244 (−3.44)	231 (+11.35)	216 (+6.23)	195 (−9.92)	190 (−10.25)
(3)	288 (+2.94)	277 (+2.50)	243 (+1.18)	227 (−16.45)	201 (−1.01)	191 (+1.10)	Negative
(4)	288 (+2.65)	280 (+2.57)	244 (−2.85)	230 (+10.45)	215sh (+1.35)	199 (−4.91)	Negative
(5)	289 (+3.00)	279 (+2.25)	243 (−1.50)	226 (−12.99)	208 (+1.02)	193 (−3.40)	Negative
(6)	284 (+3.52)	274 (+3.84)	236 (+4.62)	221 (−7.28)	214sh (−4.5)	198 (+1.94)	Negative
(7)	287sh (+2.60)	279 (+2.79)	240 (−4.15)	231 (+3.33)		196 (−5.81)	
(9)	321 (−5.30), 293 (+4.30), 277 (−3.30), 256 (+3.50), 229 (+57.86), 202 (−11.26), negative at shorter wavelengths						

[a] C.d. spectra were recorded in acetonitrile except for (7) (ethanol).

EXPERIMENTAL

Compounds (1)—(5), (7), and (9) were prepared from natural vincamine (6) [35] by known methods; their ^{1}H and ^{13}C n.m.r. spectra will be published separately.[36] The m.p.s were identical with those already published: vincane (1), 84—96 °C; [37] vincanol (2), 171—174 °C; [38] isovincanol (3), 105—108 °C; [38] deoxyvincamine (4), 164 °C; [39] epideoxyvincamine (5), 125 °C; [39] vincaminol (7), 180 °C; [40] vincamone (9), 170—172 °C.[38]

The c.d. spectra were measured with a Mark III dichrograph (Jobin-Yvon), connected on-line to a PDP-8 computer, at room temperature in cells of 0.01—2.00 cm pathlength and at concentrations of *ca.* 1 mg cm^{-3}.

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