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# THE OPTICAL ROTATORY DISPERSION AND CIRCULAR DICHROISM OF THE PHTHALIDEISOQUINOLINE ALKALOIDS AND OF THEIR α-HYDROXYBENZYLTETRAHYDROISOQUINOLINE DERIVATIVES[1]

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**Abstract**—The phthalideisoquinoline alkaloids include hydrastine and narcotine. The UV, ORD and CD curves of a range of these compounds have been studied. Each alkaloid contains two chromophoric groups—the tetrahydroisoquinoline (*T*) and phthalide (*P*) groups; each of these contains one single centre of chirality, by which it is chiefly perturbed.

The compounds fall into two main classes, those with 1*R*, 9*R* and 1*R*, 9*S* configurations, and the enantiomers of each class. The compounds generally carry substituents at positions 6, 7, 3′, 4′, each pair (6,7; 3′,4′) consisting of two OMe groups or a methylene-dioxy group; as expected, differences between substituents of this kind do not alter the general pattern of curves but do affect the quantitative values.

Representative model compounds containing the tetrahydro-isoquinoline and phthalide chromophores separately have been prepared and their UV, CD and ORD curves measured.

Attempts have been made to relate the CD of the alkaloids to the absorption bands of the two separate chromophores, and the tentative results are presented here with some reservations.

The superficial appearance of the ORD curves is no more complex than that of the CD curves; in our present empirical state of knowledge ORD may also be useful for allotment of configuration.

The introduction of an additional OMe group at C-8 makes little difference to the ORD and CD curves.

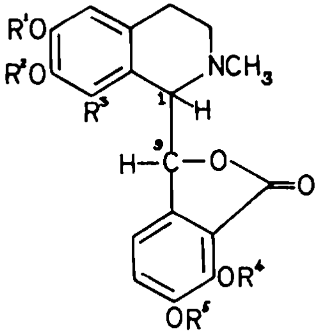
The diols, obtained by reductive opening of the lactone ring, are much more flexible than the original alkaloids; only empirical comparison of the ORD and CD curves is possible.

## INTRODUCTION

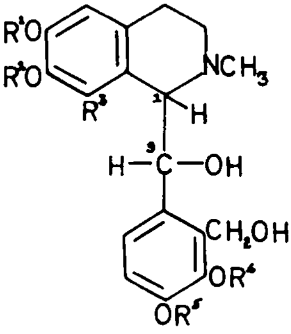
IN AN earlier paper from Olomouc[2] an attempt was made to elucidate the relative and the absolute configuration of the phthalideisoquinoline alkaloids (I), their diols (II), and of some model compounds, on the basis of the dissociation constants, the $R_f$-values (paper and TLC) the optical rotation in the visible region, and IR spectral data. These problems have also been studied by other groups of workers[3-8] using a variety of methods. (For a summary of earlier work see Ref. 9).

The purpose of the present work was to confirm our earlier findings by detailed analysis of the ORD and CD data. More accurate measurements of some dissociation constants have been carried out. TLC was carried out with different solvent systems, and the results are supplementary to those given in the earlier paper.[2]

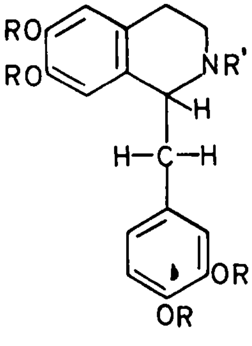
The phthalideisoquinoline alkaloids (I) and their α-hydroxybenzyltetrahydroisoquinoline derivatives (II) are analogues of the 1-benzyltetrahydroisoquinolines (III).



I



II



III

The absolute configuration at C-1 of a 1*S* compound of type III is the same as that of a 1*R*-phthalide alkaloid (I; or its derivatives II), because the presence of an oxygen atom at C-9 in I alters the precedence of groups at C-1 under the Sequence Rule.[10]

The ORD curves of the hydrastines (Ig) and of the narcotines (Ih, j)[3,11] and of bicuculline[12] at longer wavelengths have been reported previously, but the correlation of these curves with the absolute configurations has not been fully discussed.

*Summary of CD and ORD results*

CD curves were measured at Bonn with the early model Jouan Dichrographe, in dioxan and methanol; and later with the newer Dichrographe (Model CD 185) in ethanol, acetonitrile, aqueous N HCl and (some compounds only) in methycyclohexane. In most cases the Δε values in dioxan were greater than those in methanol. ORD curves were measured at Westfield in methanol.

UV absorptions were measured at Olomouc in ethanol, and Westfield in methanol (using the solutions employed for ORD measurements), and at Bonn with a Cary 14 spectrophotometer (using the solutions employed for the CD measurements).

The results are summarised in Table 1 for the alkaloids and Table 2 for the diols obtained by reductive opening of the lactone ring. Specimen CD curves are given in Figs. 1 and 2. (For ORD curves see later, p. 21).

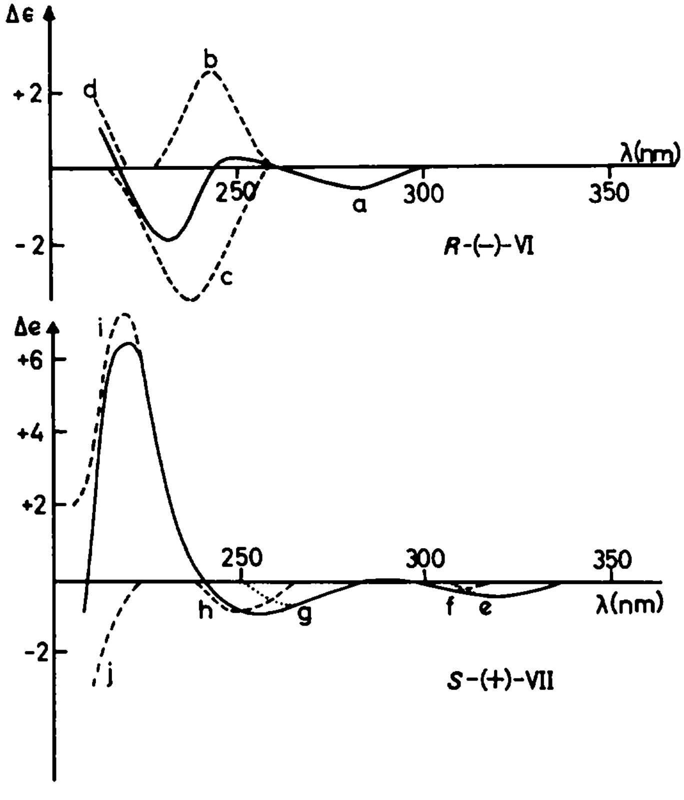


FIG. 1 CD curves of the reference compounds R-(−)-VI and S-(+)-VII in ethanol (———), with resolution into partial bands (- - - -); see text p. 5072.

The C.D. curves of the alkaloids, whose maxima are presented in Table 1, have been resolved by inspection into Gaussian-shaped partial bands, designated by lower-case letters ("a" to "j"). This band analysis has been done for all cases where the halfband-width was unusually great or where a shoulder appeared at least in one solvent. The results are summarized graphically in Figs. 3 (for ethanol solution), 4 (acetonitrile), 5 (N HCl), and 6 (methylcyclohexane); typical examples for the curve-resolution (capnoidine and bicuculline in ethanol solution) are shown in Figs. 7 and 8. Subsequent

TABLE 1. CD AND ORD OF

| No. | Compound | Position | $R^1$ 6 | $R^2$ 7 | $R^3$ 8 | $R^4$ 3′ | $R^5$ 4′ | Configuration | (Ethanol) λ (nm) | Δε |
|---|---|---|---|---|---|---|---|---|---|---|
| Ia | Bicuculline | | —$CH_2$— | | — | —$CH_2$— | | 1*S*, 9*R* | 322·5 | +3·25 |
| | | | | | | | | | 310i | +2·50 |
| | | | | | | | | | 266i | +2·52 |
| | | | | | | | | | 250 | +3·84 |
| | | | | | | | | | 235i | −2·98 |
| | | | | | | | | | 223 | −13·7 |
| | | | | | | | | | 215i | −6·23 |
| | | | | | | | | | 207 | +18 |
| Ib | Adlumidine | | —$CH_2$— | | — | —$CH_2$— | | 1*S*, 9*S* | 330 | −0·63 |
| | | | | | | | | | 297 | −2·35 |
| | | | | | | | | | 259·5i | −1·38 |
| | | | | | | | | | 249 | −4·11 |
| | | | | | | | | | 233 | +6·18 |
| | | | | | | | | | 222 | +7·07 |
| | | | | | | | | | 212i | +14 |
| | | | | | | | | | 206 | +16 |
| | | | | | | | | | 202 | 0 |
| Ic | Capnoidine | | —$CH_2$— | | — | —$CH_2$— | | 1*R*, 9*R* | 327·5 | +0·65 |
| | | | | | | | | | 296·5 | +2·42 |
| | | | | | | | | | 260i | +1·07 |
| | | | | | | | | | 249 | +4·02 |
| | | | | | | | | | 234i | −7·92 |
| | | | | | | | | | 224i | −9·75 |
| | | | | | | | | | 208·5 | −19 |
| Id | Corlumine | | $CH_3$ | $CH_3$ | — | —$CH_2$— | | 1*S*, 9*R* | 325 | +2·57 |
| | | | | | | | | | 291·5 | −0·45 |
| | | | | | | | | | 268 | +1·60 |
| | | | | | | | | | 255·5i | +0·85 |
| | | | | | | | | | 235i | −17·11 |
| | | | | | | | | | 226 | −25·36 |
| | | | | | | | | | 215i | −10·5 |
| | | | | | | | | | 205 | +39 |

PHTHALIDE ISOQUINOLINE ALKALOIDS

| Circular Dichroism | | | | | | | | ORD (MeOH) | |
|---|---|---|---|---|---|---|---|---|---|
| (Acetonitrile) | | (N HCl) | | (Methylcyclohexane) | | (Dioxan) | | Wavelengths of extrema (nm) | Amplitude of Cotton effect ($a \times 10^{-2}$) |
| λ (nm) | Δε | λ (nm) | Δε | λ (nm) | Δε | λ (nm) | Δε | | |
| 321·5 | +3·66 | 323 | +0·95 | 316i | +3·24 | 314 | +4·4 | 332/318 | +49 |
| 311i | +2·84 | 310i | +0·70 | 306·5 | +3·66 | 270 | +2·0 | 300/278 | −69 |
| 266·5 | +2·83 | 291·5 | −1·49 | 282·5i | +1·79 | 267 | +3·6 | 258/234 | +264 |
| 248 | +5·00 | 257i | −2·46 | 272·5 | +3·01 | 261 | +3·4 | | |
| 234i | +0·78 | 245i | −7·82 | 263·5 | +3·23 | 240 | +6·6! | | |
| 222 | −8·66 | 227 | −30·18 | 255 | +3·00 | | | | |
| 213i | −2·83 | 215·5 | −6·2 | 241 | +4·90 | | | | |
| 207 | +14 | 207 | +47 | 228·5 | +2·9 | | | | |
| | | | | 216·5 | −3·2 | | | | |
| | | | | 204 | +19·5 | | | | |
| | | | | 195 | 0 | | | | |
| | | | | | | | | | |
| 331 | −0·65 | 325 | −1·83 | 323 | −1·25 | 340 | −0·2 | 338/317 | −32 |
| 296 | −4·15 | 282·5 | −0·77 | 294·5 | −3·35 | 295 | −2·1 | 303/281 | −88 |
| 263·5i | −1·77 | 272i | −0·81 | 263·5 | −2·22 | 271 | −0·6 | 254/239 | −279 |
| 248 | −6·38 | 250·5 | −5·54 | 248 | −3·63 | 248 | −4·2 | | |
| 229·5 | +10·80 | 237i | +3·69 | 233 | +5·3 | 232 | +6! | | |
| 217i | +10·13 | 224 | +24 | 223 | +12 | | | | |
| 208 | +25 | 218i | +16 | | | | | | |
| | | 207 | −21 | | | | | | |
| | | | | | | | | | |
| 331·5 | +0·34 | 325·5 | +1·69 | 324·5 | +0·74 | 325 | +0·4 | 334/320 | +5 |
| 296·5 | +2·37 | 305i | +1·05 | 295 | +3·32 | 293 | +2·2 | 303/283 | +86 |
| 261i | +1·15 | 281·5 | +0·56 | 272·5 | +0·54 | 270 | +0·2 | 236/240 | +239 |
| 248 | +3·72 | 250·5 | +4·99 | 263 | +1·11 | 250 | +2·2 | | |
| 232 | −7·34 | 238·5 | −3·61 | 254·5i | +1·36 | | | | |
| 214i | −10·95 | 224 | −26·84 | 248 | +2·11 | | | | |
| 207 | −18 | 207 | +20 | 245i | +1·60 | | | | |
| | | | | 234 | −7·38 | | | | |
| | | | | 212 | −30 | | | | |
| | | | | 197 | +17 | | | | |
| | | | | | | | | | |
| 324 | +2·62 | 330 | +0·82 | 317 | +2·30 | 320 | +3·4 | 336/316 | +63 |
| 291·5 | −0·35 | 305i | +0·40 | 299i | +1·32 | 290 | +0·8 | 297/279 | −45 |
| 267 | +1·98 | 285·5 | −1·81 | 284 | +1·33 | 268 | +3·2 | 256/242 | +277 |
| 257i | +1·52 | 248i | −10·91 | 273 | +2·72 | 234 | −12 | | |
| 236i | −11·30 | 228 | −43·27 | 264·5 | +2·83 | | | | |
| 226 | −15·47 | 217i | −16 | 257 | +2·22 | | | | |
| | | 205 | +77 | 247·5 | +1·40 | | | | |
| | | | | 235 | −5·5 | | | | |
| | | | | 223·5 | −6 | | | | |
| | | | | 213 | −4·1 | | | | |
| | | | | 203 | +20 | | | | |

| No. | Compound | | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | Configuration | (Ethanol) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Position | 6 | 7 | 8 | 3′ | 4′ | | λ(nm) | Δε |
| Ie | Corlumidine | | H | $CH_3$ | — | $—CH_2—$ | | 1*S*, 9*R* | 324 | +2·37 |
| | | | | | | | | | 310i | +1·68 |
| | | | | | | | | | 270 | +1·81 |
| | | | | | | | | | 250·5 | +2·22 |
| | | | | | | | | | 237i | −10·02 |
| | | | | | | | | | 227 | −16·03 |
| | | | | | | | | | 214 | −4·7 |
| | | | | | | | | | 207 | +28 |
| If | Adlumine | | $CH_3$ | $CH_3$ | — | $—CH_2—$ | | 1*S*, 9*S* | 323 | −2·07 |
| | | | | | | | | | 292 | −4·49 |
| | | | | | | | | | 261i | −2·32 |
| | | | | | | | | | 246 | −9·29 |
| | | | | | | | | | 228·5i | +0·87 |
| | | | | | | | | | 208·5 | +20 |
| Ig | α-Hydrastine | | $—CH_2—$ | | — | $CH_3$ | $CH_3$ | 1*R*, 9*R* | 307* | +1·94* |
| | | | | | | | | | 278 | −1·01 |
| | | | | | | | | | 256 | +0·34 |
| | | | | | | | | | 233 | −9·8 |
| Ih | β-Hydrastine | | $—CH_2—$ | | — | $CH_3$ | $CH_3$ | 1*R*, 9*S* | 311 | −2·76 |
| | | | | | | | | | 266 | −1·73 |
| | | | | | | | | | 239 | +6·47 |
| | | | | | | | | | 217 | +15·64 |
| | | | | | | | | | 203 | −45·8 |
| Ij | α-Narcotine | | $—CH_2—$ | | $OCH_3$ | $CH_3$ | $CH_3$ | 1*R*, 9*S* | 314 | −4·11 |
| | | | | | | | | | 305·5i | −3·35 |
| | | | | | | | | | 253i | −4·79 |
| | | | | | | | | | 235·5 | −14·22 |
| | | | | | | | | | 228 | −25·5 |
| | | | | | | | | | 218·5 | −25 |
| Ik | β-Narcotine | | $CH_2$-- | | $OCH_3$ | $CH_3$ | $CH_3$ | 1*R*, 9*R* | | |

*Methylcyclohexane*

On account of the low solubility of the alkaloids in this solvent their concentrations were determined approximately from their UV absorption on the assumption that the *absorption* coefficients in ethanol and methyl cyclohexane are similar.

| Circular Dichroism | | | | | | | | ORD (MeOH) | |
|---|---|---|---|---|---|---|---|---|---|
| (Acetonitrile) | | (N HCl) | | (Methylcyclohexane) | | (Dioxan) | | Wavelengths of extrema (nm) | Amplitude of Cotton effect $(a \times 10^{-2})$ |
| λ (nm) | Δε | λ (nm) | Δε | λ (nm) | Δε | λ (nm) | Δε | | |
| 324 | +2·55 | 335 | +0·11 | | | | | 343/325 | +52 |
| 310i | +1·9 | 286 | −1·50 | | | | | 300/283 | −59 |
| 291·5 | −0·43 | 253i | −6·25 | | | | | 256/240 | +302 |
| 267 | +2·20 | 228 | −37·30 | | | | | | |
| 248 | +2·20 | 216i | −12 | | | | | | |
| 233·5i | −9·3 | 206 | +25 | | | | | | |
| 224 | −16·47 | | | | | | | | |
| 212 | −6·20 | | | | | | | | |
| 205 | +19 | | | | | | | | |
| | | | | | | | | | |
| 325·5 | −1·35 | 328 | −2·48 | 318 | −1·75 | 315 | −2 | 337/315 | −41 |
| 292·5 | −3·45 | 278 | −1·00 | 294 | −4·49 | 307 | −1·6 | 301/278 | −111 |
| 260·5i | −1·76 | 249 | −5·91 | 258·5i | −2·06 | 292 | −5 | 254/236 | −397! |
| 246 | −7·21 | 241 | −6·42 | 246 | −8·26 | 272 | −1·6 | | |
| 228·5 | −1·31 | 223 | +29·78 | 230·5 | −2·96 | 247 | −12·8 | | |
| 222 | −3·19 | 208 | −30 | 215 | +26 | | | | |
| 206 | +23·5 | | | | | | | | |
| | | | | | | | | | |
| | | | | | | 298 | +5·77 | | |
| | | | | | | 275 | −1·93 | | |
| | | | | | | 236 | −29·1 | | |
| | | | | | | | | | |
| 310 | −3·24 | 312 | −1·92 | 311i | −2·96 | 306 | −4 | 325/310 | −63 |
| 267 | −2·40 | 288·5 | +2·38 | 304 | −4·15 | 289 | −2·4 | 296/279 | +40 |
| 262 | −2·34 | 250i | +7·68 | 298i | −3·41 | 270 | −3·7 | | |
| 237i | +3·54 | 222 | +38·18 | 288·5 | −2·55 | | | | |
| 219 | +11·25 | 215i | +29·73 | 275 | −3·33 | | | | |
| | | | | 265 | −3·59 | | | | |
| | | | | 257i | −2·95 | | | | |
| | | | | 241·5 | +1·07 | | | | |
| | | | | 226·5 | −2·01 | | | | |
| | | | | 211 | +4·8 | | | | |
| | | | | 205 | −16 | | | | |
| | | | | | | | | | |
| 311·5 | −3·71 | 314·5 | −2·51 | 306·5 | −2·88 | 311 | −5·3 | 325/? | — |
| 301·5i | −2·68 | 303i | −1·72 | 272·5i | −1·86 | 286 | −0·2 | 296/268 | +112 |
| 271i | −3·31 | 285i | +1·08 | 263i | −2·71 | 234 | −20·3 | | |
| 258i | −4·68 | 254 | +2·36 | 252i | −4·68 | | | | |
| 233 | −14·91 | 224 | +22 | 238·5 | −10·25 | | | | |
| | | 215 | −10 | 226 | −11·66 | | | | |
| | | | | | | | | | |
| | | | | | | 329 | +0·2 | | |
| | | | | | | 302 | −1·6 | | |
| | | | | | | 274 | +1·7 | | |

*Dioxan*
CD measurements in this solvent are all with the early Jouan Dichrographe.

* Indicated CD in methanol (*not* ethanol); measured on early Dichrographe.

TABLE 2. SUMMARY OF CD AND ORD DATA FOR α-HYDROXYBENZYL-TETRAHYDROISOQUINOLINES ("DIOLS")

| No. | Compound<br>Position | $R^1$<br>6 | $R^2$<br>7 | $R^3$<br>8 | $R^4$<br>3′ | $R^5$<br>4′ | Configuration | C.D. (MeOH) | | C.D. (dioxan) | | ORD (MeOH) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | $\lambda$ (nm) | $\Delta\varepsilon$ | $\lambda$ (nm) | $\Delta\varepsilon$ | Wavelengths of extrema (nm) | Amplitude of Cotton effect ($a \times 10^{-2}$) |
| IIa | Bicuculine diol | $—CH_2$ | — | — | $—CH_2—$ | | 1*S*, 9*R* | 296 | −2·2 | 300 | −2·2 | 300/284 | −89 |
| | | | | | | | | 279 | −0·4 | 280 | 0 | | |
| | | | | | | | | 250 | −3·3 | | | | |
| IIb | Adlumidine diol | $—CH_2$ | — | — | $—CH_2—$ | | 1*S*, 9*S* | 295 | +2·2 | 295 | +0·8 | 298/286 | +22 |
| | | | | | | | | 278 | −1·4 | 257 | −0·8 | | |
| IIc | Capnoidine diol | $—CH_2$ | — | — | $—CH_2—$ | | 1*R*, 9*R* | 297 | −1·5 | 295 | −0·7 | 301/288 | −38 |
| | | | | | | | | 280 | +0·6 | 278 | +1·0 | | |
| IIe | Corlumidine diol | H | $CH_3$ | — | $—CH_2—$ | | 1*S*, 9*R* | | | | | 299/281 | −66 |
| IIg | α-Hydrastine diol | $—CH_2$ | — | — | $CH_3$ | $CH_3$ | 1*R*, 9*R* | 291 | +1·89 | 292 | +2·24 | | |
| | | | | | | | | 245 | −7·5 | 246 | −5·4 | | |
| | | | | | | | | a* | + + | a* | + + | | |
| IIh | β-Hydrastine diol | $—CH_2$ | — | — | $CH_3$ | $CH_3$ | 1*R*, 9*S* | | | | | 300/181 | +112 |
| IIj | α-Narcotine diol | $—CH_2$ | — | $OCH_3$ | $CH_3$ | $CH_3$ | 1*R*, 9*S* | | | 287 | +0·9 | 300/283 | +20 |
| | | | | | | | | | | 249 | −3·7! | | |
| IIk | β-Narcotine diol | $—CH_2$ | — | $OCH_3$ | $CH_3$ | $CH_3$ | 1*R*, 9*R* | 304 | −0·4 | 284 | +0·9 | 292/? | negligible |
| | | | | | | | | 283 | +0·5 | 244 | −3·2 | | |
| | | | | | | | | 245 | −4 | | | | |

(a)*—at shorter wavelengths

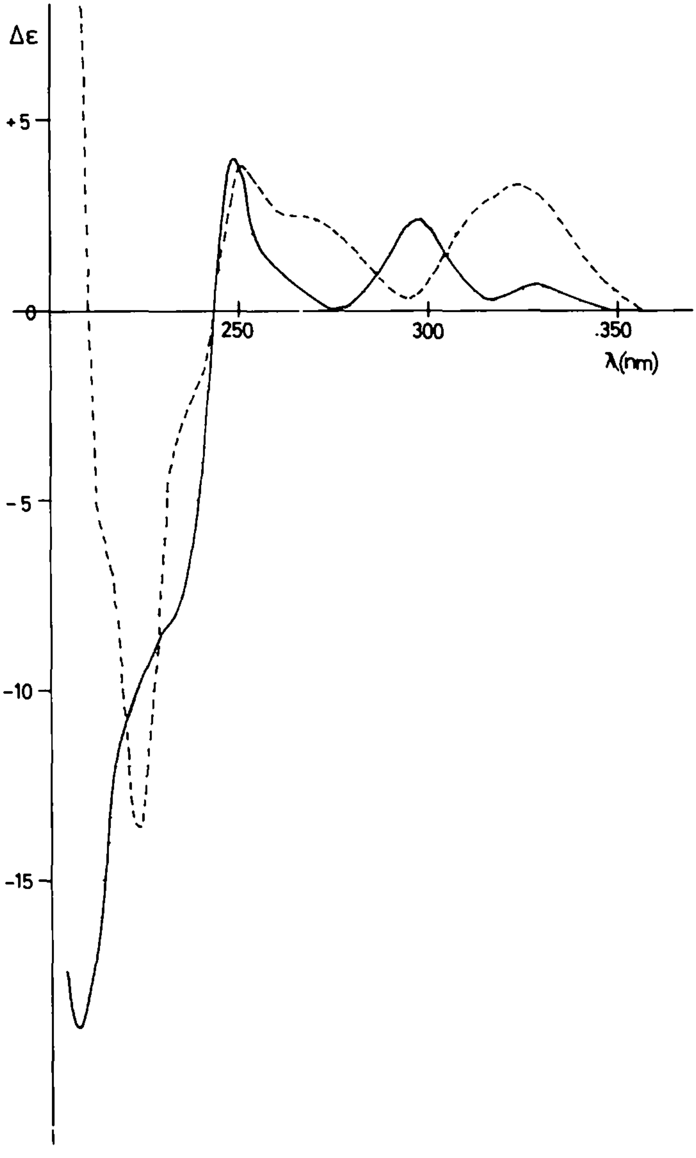


FIG. 2 CD curves of capnoidine (Ic) (———) and bicuculline (Ia) (– – – – –) in ethanol.

correlations are attempted, wherever possible, between the stereochemistry of the alkaloids and these partial bands, rather than with the CD curves as measured. It is, however, also possible to determine the configuration at C-1 and C-9 by inspection of the experimental CD or ORD curves (see pp. 14, 21). The CD curves in methanol and acetonitrile are in general very similar to those in ethanol solution. We therefore discuss the ethanol curves in detail, and refer to the other two solvents only in those cases where there are major differences.

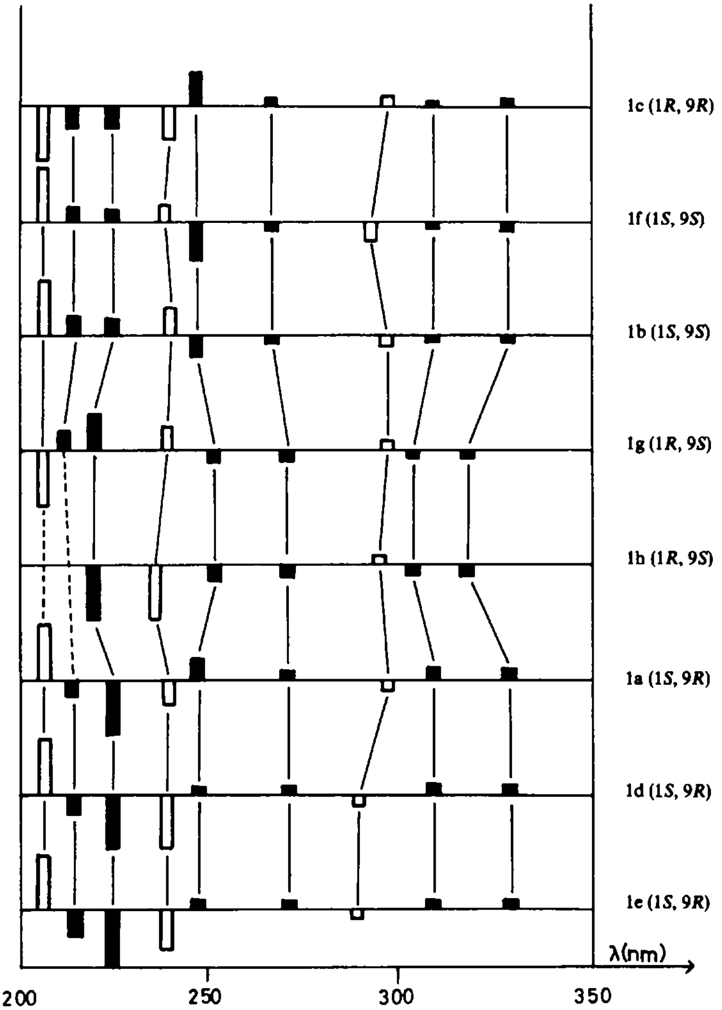
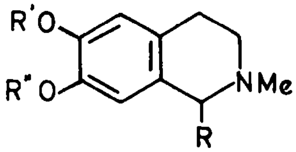


FIG. 3 Schematic diagram of partial CD bands of lactone alkaloids (in ethanol). Length of bars shows qualitatively magnitude of partial CD bands; black bars for *P*-bands, white bars for *T*-bands.

### *Reference compounds*

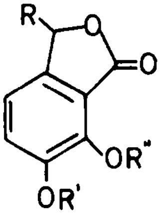
Phthalideisoquinoline alkaloids (as I) contain in the same molecule two types of aromatic chromophores, viz:- the tetrahydroisoquinoline ("*T*") system (IV) and the phthalide ("*P*") system (V). We therefore prepared optically active reference compounds (VI and VII) each containing only one chromophore, and determined their CD and ORD curves.

The racemic tetrahydroisoquinoline (VI) was obtained from Dr. K. Bernauer (Basel), who used this compound in his synthesis[13] of (±)-pronuciferine. Resolution of the base (VI) by crystallization of its salt with (+)-tartaric acid from acetone gave the (−)-enantiomer, $[\alpha]_D^{20}$, −30·6°. The CD curve of (−)-VI in ethanol showed four



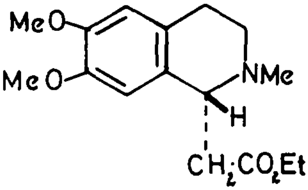
IV

"*T*" System

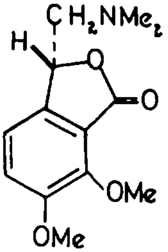


V

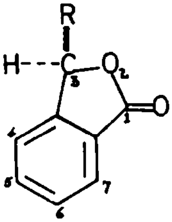
"*P*" System



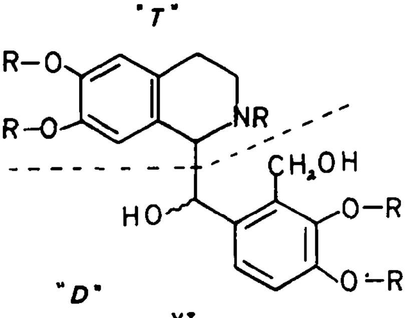
VI



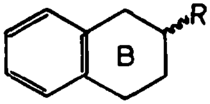
VII



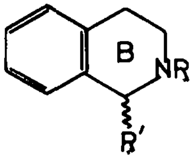
VIII



XI



IX



X

bands ("a": 285 nm, $\Delta\varepsilon$ −0·61; "b": 247 nm, $\Delta\varepsilon$ +0·21; "c": 232 nm, $\Delta\varepsilon$ −2·14; another positive band "d" at shorter wavelength).

In N HCl solution the small positive band at 247 nm could not be detected; no measurements were possible below 210 nm. These bands cannot be further resolved into partial bands. The absolute configuration shown is allotted by analogy with 1*R*-substituted tetrahydroisoquinolines (carrying oxygen substituents at 6 and 7), which all show two negative CD (or CRD) Cotton effects in ethanol.[11,14–16] (The shorter wavelength CD band of (−)-VI changes sign in dioxan or isopropanol).

The racemic phthalide (VII) was prepared from opianic acid by condensation with nitromethane and reduction to an aminomethylphthalide,[17] followed by Leuckart–Wallach methylation.[18] The product was resolved by forming either the (+)-dibenzoyltartrate (in acetone-light petroleum) or the (−)-malate (in ethyl acetate-methanol); the products obtained showed maximal rotations $[\alpha]_D$ +36·5° and −37·8° respectively. The CD curves were of mirror-image character; (−)-VII in ethanol showed three positive CD bands at 315, 256, and 201 nm ("j") ($\Delta\varepsilon$: +0·26, +0·69 and +7·0) and a strong negative band at 219 nm ("i") ($\Delta\varepsilon$: −7·0). Studies on the phthalide-alkaloids (p. 14) showed that the 315 nm band was due to the phthalide (*P*) system, and that a positive CD maximum here indicated the *R* configuration; (−)-VII is therefore the *R*-isomer.

The two bands at longest wavelengths could each be resolved into a pair of partial bands of the same sign ("e": 315; "f": 302; and "g": 260; "h": 248 nm).

The absolute configuration of the unsubstituted benzylphthalide (VIII; R = $CH_2Ph$) has been determined by Berti *et al.*,[19] and ORD and CD curves have been measured on a sample kindly provided by Prof. Berti (Pisa).

Two other simple optically-active phthalides (VIII; R = Me or Bu) have been studied by Nagi *et al.*,[20] who measured ORD curves only down to 300 nm. Through the courtesy of Prof. Mitsuhashi we have now been able to measure the CD curve of the *S*(−)-butyl compound (*ent*-VIII; R = Bu); this showed one band system at about 260 nm ($^1L_b$ and/or n → π* of lactone group; shows fine structure) and the conjugation band at about 220 nm (overlapping the $^1L_a$-band?).

Since compounds (VIII; R = $CH_2Ph$ and Bu) lack the two OMe groups in the phthalide ring, band positions and CD values cannot be compared with those for compound (VII).

## *Discussion of lactones*

*Introduction.* As a first approximation we assume that the two chromophores, the "*T*-" and "*P*-" systems, do not interact with each other (no vicinal effects), so that their effects can be treated as additive. The band positions in the UV and CD spectra should then be roughly the same as for the reference compounds (VI and VII).

The following transitions would be expected (cf. Scott[21]) for the *T*-system.

$^1L_b$ ($^1B_{2u}$) at about 280 nm
$^1L_a$ ($^1B_{1u}$) at about 230 nm
$^1B$ ($^1E_{2u}$) at about 200 nm

An electron-transfer band from the alkoxy groups to the aromatic ring is also expected.

The corresponding bands for the *P*-system probably appear at slightly longer wavelenths than the *T*-bands, because of the conjugation of the CO group with the

TABLE 3. UV ABSORPTION SPECTRA

All values are in ethanol and are presented as λ(max or min) in nm with log ε in parentheses.

(A) Alkaloids; lactones

| Compound | No. | Max | Min | Max | Max (Sh.) | Min | Max | Min | Max |
|---|---|---|---|---|---|---|---|---|---|
| Bicuculline | Ia | 202(4·74) | 217(4·46) | 221(4·47) | 238(4·09) | 263(3·04) | 298(3·76) | 310(3·62) | 325(3·72) |
| Adlumidine | Ib | 200(4·69) | 215(4·45) | 220(4·47) | 236(4·12) | 262(3·11) | 294(3·79) | 307(3·63) | 323(3·73) |
| Capnoidine | Ic | 200(4·68) | 215(4·44) | 220(4·47) | 235(4·13) | 263(3·33) | 294(3·85) | 307(3·72) | 323(3·78) |
| Corlumine | Id | 202(4·75) | 215(4·50) | 220(4·51) | 236(4·16) | 260(3·29) | 286(3·66) | 298(3·49) | 320(3·74) |
| Adlumine | If | 201(4·45) | 215(4·22) | 220(4·24) | 236(3·93) | 260(3·02) | 286(3·38) | 299(3·22) | 324(3·45) |
| β-Hydrastine* | Ih | 202(4·79) | — | 218(4·53) | 238(4·15) | 263(3·14) | 298(3·86) | — | 316(3·63) |
| α-Narcotine | Ij | 209(4·83) | — | — | 237(4·19) | 263(3·28) | 289(3·60) | 294(3·59) | 308(3·69) |
| β-Narcotine | Ik | 211(4·77) | — | — | 237(4·20) | 260(3.23) | 291(3·56) | 295(3·54) | 312(3·66) |
| Corlumidine | Ie | — | — | — | 235(4·11) | 262(3·18) | 290(3·70) | 302(3·52) | 323(3·73) |

(B) Related Diols

In these diols the maxima found for the lactones at about 220 nm. and 320 nm. are absent

| Compound | No. | Max | Max | Min | Max |
|---|---|---|---|---|---|
| Bicuculline diol | IIa | 205(4·76) | 233(3·98) | 264(3·49) | 291(3·92) |
| Adlumidine diol | IIb | — | 237(3·92) | 263(3·43) | 292(3·91) |
| Capnoidine diol | IIc | — | 237(3·92) | 262(3·34) | 292(3·91) |
| Corlumine diol | IId | 205(4·80) | 234(3·98) | 263(3·50) | 288(3·80) |
| Adlumine diol | IIf | — | 230(4·03) | 260(3·08) | 288(3·78) |
| β-Hydrastine diol | IIh | 205(4·92) | 236(4·18) | 260(3·28) | 287(3·88) |
| α-Narcotine diol† | IIj | 205(4·82) | 235(4·24) | 262(3·33) | 281(3·59) |
| Corlumidine diol | IIe | — | 236(3·93) | 261(3·15) | 287(3·86) |

* α-Hydrastine (Ig); very similar to β-Hydrastine

† β-Narcotine diol (IIk); very similar to α-Narcotine diol.

aromatic ring. Furthermore, the *P* system should give rise to an electron-transfer band and an n → π* band for the CO group.

### *UV and CD of reference compounds*

The UV spectrum of VI (in methanol) showed absorption maxima at 283 and 202 nm and an inflection around 223 nm; this latter corresponds to the 231 nm band in the CD. These band positions agree quite well with the pattern suggested above; the electron-transfer band is not resolved in the UV spectrum, but can be detected in the CD spectrum at 247 nm. Tentatively we assign the "a"-band $^1L_b$ character, "b" as electron-transfer band, "c" as $^1L_a$ and "d" as one of the two partial bands of the otherwise degenerate $^1B$ band. The bands named "a" and "d" are also found in all CD spectra of the alkaloids, whereas "b" and "c" cannot always be detected.

The UV spectrum of the phthalide (VII) in methanol shows a strong band at 212 nm, an inflection at about 235 nm and a band of medium intensity at 309 nm. In the CD spectrum the maxima between 220 and 300 nm do not coincide with those of the isotropic absorption spectrum in the same solvent. Presumably the overlapping of CD bands of opposite or same sign gives a pattern which is more split than in the UV spectrum.

On the latter basis the following tentative assignments are proposed; "e" and "f": electron-transfer and $^1L_b$ bands characteristic of benzoic acid derivatives with oxygen substituents in the *o*- and *m*- positions;[21a] "g": this band may correspond to the n → π* transition of the lactone group, because it is found at roughly the same position in conjugated unsaturated acids[22] (the *R*-band of conjugated enones and of acetophenones coincide as well[23, 24]) furthermore it shows fine structure in the non-polar solvent methycyclohexane; "h": $^1L_a$ and/or principal electron-transfer band (of the benzoic acid chromophore); "i" and "j": the two partial bands of opposite sign (and same magnitude) of the otherwise degenerate $^1B$ band. Bands designated as "e", "g", "h", and "i" are found in the CD spectra of all the alkaloids investigated, "f" only occasionally; "j" occurs at a shorter wavelength than "d", and cannot be detected in the CD spectra of the alkaloïds. Sometimes in the latter, additional small bands occur between bands "a" and "e" (band "f"?), as well as between 210 and 240 nm.

### *General consideration of phthalideisoquinoline UV and CD curves*

According to this scheme, and assuming no vicinal effects, the UV spectrum of a phthalideisoquinoline alkaloid might be expected to show the bands of both systems. The observed UV spectrum of, e.g., capnoidine in methanol, has absorption maxima at the following wavelengths: 325, 294, 235, 220, and 200 nm; this is in reasonable agreement with a superposition of the spectra of the "*T*" and "*P*" systems, if one allows for a small red-shift of the two bands at longest wavelengths.

The CD curves of the alkaloids in ethanol or acetonitrile can be resolved into six to eight partial bands; see Figs. 3 and 4, which also indicate the suggested "parentage" of the partial bands. From these Figures it can be seen that in the CD spectra of all the 6,7,3′,4′-tetrasubstituted alkaloids the partial bands "e", "a", "g", "i", and "d" (from long to short wavelengths) retain the signs of Cotton effects found for the corresponding reference compounds (VI and VII).

There is no reason *a priori* why the CD bands associated with the "*P*-" and "*T*"-chromophores should show the same magnitudes or even signs of the individual Cotton effects in the *erythro* (e.g. 1*S*, 9*R*) compounds as in those with the *threo* configuration (e.g. 1*R*, 9*R*). The Cotton effects are governed by the positions of both chromophores (in the preferred conformations of the molecule) relative to the chiral centres 1 and 9. The contributions of individual atoms might not be similar in the two diastereoisomers. Nevertheless, the empirical CD data for *erythro* [(1*S*, 9*R*) and (1*R*, 9*S*)] compounds are consistent with the *same* sign pattern for the CD bands of both chromophores as in the *threo* [(1*R*, 9*R*) and (1*S*, 9*S*)] series.

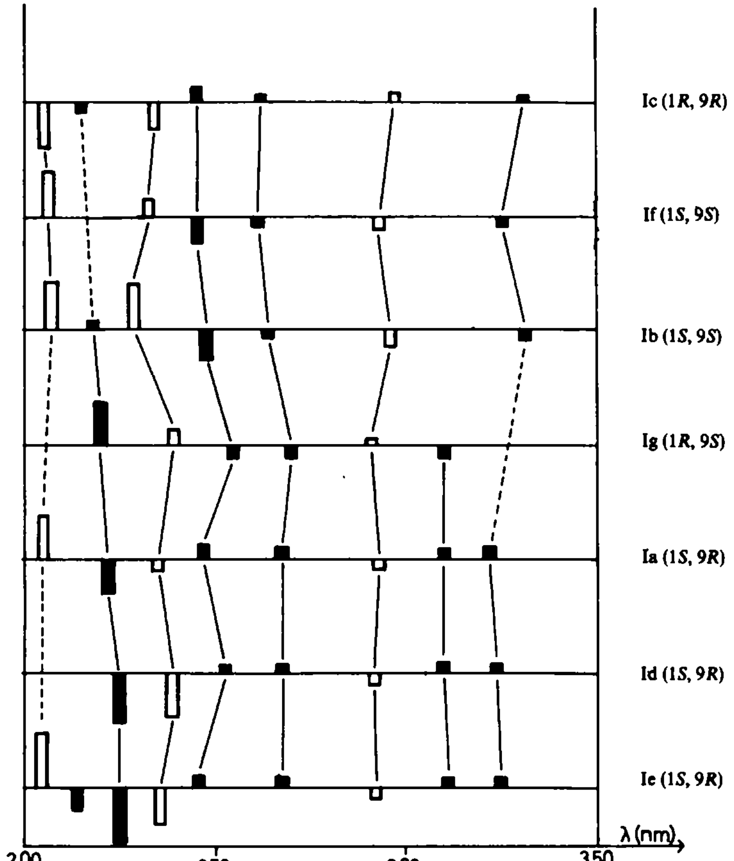


FIG. 4 Schematic diagram of partial CD bands of lactone alkaloids (in acetonitrile). Meaning of bars as in Fig. 3.

For the (1*R*)-configuration, characteristic partial bands are a positive band at about 290 nm and a strong negative one at about 205 nm. The (9*R*)-configuration is associated with positive partial bands at about 320 and 265 nm, and a strong negative one at about 225 nm. As it is highly improbable that all three bands would change their signs in going from the model compound (VII) to an alkaloid of the same absolute configuration at C-9, we feel that the absolute configuration of compound VII can be safely assigned by comparing its CD spectrum with those of the alkaloids of known chirality. These results for the different alkaloids are consistent with earlier assignments.[2-8]

Band "a" can be detected unequivocally in the CD spectrum of the alkaloids if its sign is the same as that of bands "e" and "g". If it is opposite in sign to these, it shows up as a maximum only in a polar solvent such as ethanol; whereas in non-polar solvents (methylcyclohexane or dioxan) it appears only as a minimum between the two maxima. The reason is the bathochromic shift of band "g" and the hypsochromic shift of band "e" on going from the polar to the non-polar solvent, which is in accordance with the above assignments of "e" and "g".

By simple inspection of the CD curve of an alkaloid the signs of four bands ("e", "g", "i" and "d") can easily be picked out; from the first three bands the configuration at C-9, and from the last band that at C-1 can be determined.

Hruban and Šantavý[25] have noticed a blue-shift of the UV bands at ca. 280 and 240 nm by going from a methylenedioxy to a dimethoxy compound. If this structural change occurs in the "*T*"-part of the molecule (adlumine, corlumine and corlumidine) the same blue-shift can be seen for band "a" of the CD curve. If the same structural change occurs in the "*P*" part of the molecule (β-hydrastine and α-narcotine) the blue-shift can be seen for band "e", which again supports our band-resolutions.

The band at about 238 nm which was assigned *T*-origin, is positive in 1*R-threo*, and negative in 1*R-erythro* compounds. This is probably due to the fact that two bands of opposite sign "b" and "c" merge together here (cf. the spectrum of VI, Fig. 1); their relative strengths depend on the chirality at C-9.

In acidic aqueous solution only about four bands can be detected with certainty. It is interesting to note that in the reference compound (VII) the band at longest wavelength changes the sign of its Cotton effect on protonation, whereas for the alkaloids this is not the case. As Fig. 5 shows, a correlation of the CD bands with the stereochemistry at C-1 and C-9 is possible also for this solvent.

For bicuculline (Ia) there is a great difference in band positions between the curves in methanol and dioxan, and also in the shape of the curves at shorter wavelengths. As these measurements were made on the early Dichrographe, we do not wish to emphasize them.

### *Compounds with an additional* 8-*methoxy group*

The narcotines (α and β) differ from all the compounds treated so far by the presence of an additional OMe group at C-8. This could influence the CD curves either by changing the character of the *T*-chromophore (cf. Platt,[26] Mason[27]), or by altering the preferred conformation of the *P*-system relative to the *T*-system (or in both ways).

α-*Narcotine* (1*R*, 9*S*) behaves in a fashion similar to corlumine in the long wavelength region, but the curves are, of course, of enantiomeric type. In the shorter wavelength region below 240 nm an inversion of sign occurs.

β-*Narcotine* (1*R*, 9*R*). The positive band "e" is still associated with the 9*R*-configuration. In methanol solution the bands at wavelengths longer than 260 nm correspond to those of capnoidine (with the same configuration), but band "h" cannot be detected with certainty. In dioxan a *negative* maximum appears at 302 nm. This change is perhaps due to a conformational difference in the two solvents, which might be specially associated with steric hindrance introduced by the additional OMe group.

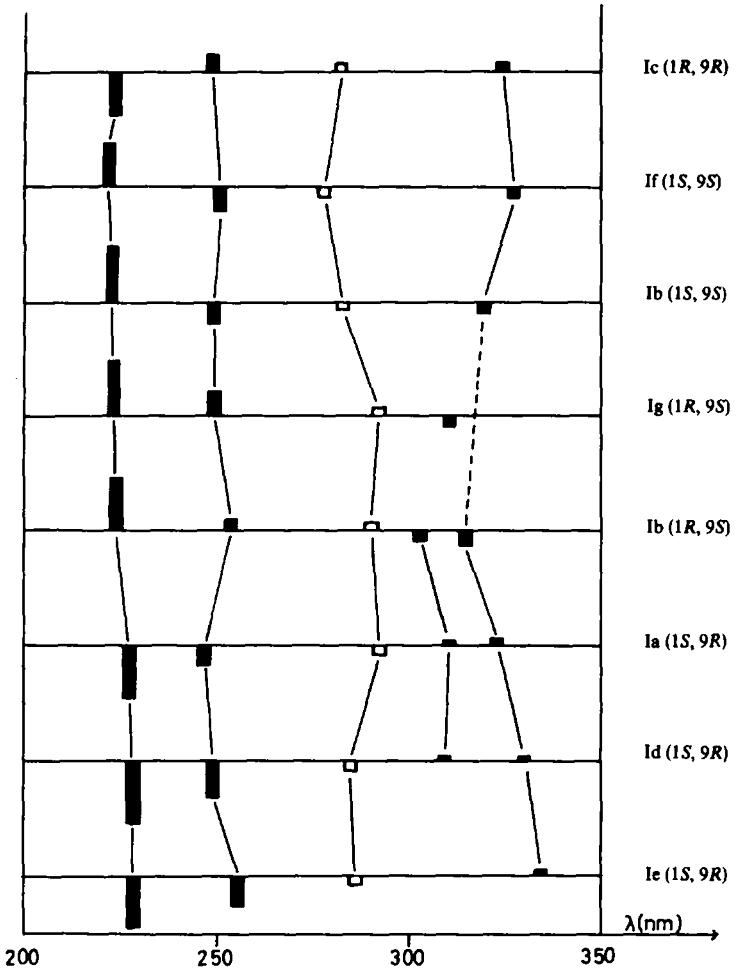


FIG. 5 Schematic diagram of partial CD bands of lactone alkaloids (in N HCl). Meaning of bars as in Fig. 3. Origin of bands below 270 nm uncertain; black bars in this range do not mean that the band is necessarily of *P*-origin.

(These measurements were made with the early Dichrographe and are only discussed qualitatively.)

### *Semi-empirical approach to a correlation between the chirality of these alkaloids and their CD curves*

Many treatments, partly in agreement, partly conflicting, have been proposed recently to correlate the chiralty of saturated ketones and the signs of their CD or ORD curves. These stem from the Octant Rule;[28] for a summary by one of us (G.S.), see a discussion of adamantanones.[29] The complexities of the situation are well illustrated by a review by Schellman[30] and a detailed consideration by Höhn and Weigang[31] of the many factors involved for even a simple saturated ketone.

One short cut through these complexities is provided by the concept of "spheres".[24]

For saturated ketones in which the second sphere (the ring into which the CO group is incorporated) is chiral, this chirality determines the sign (and to a large extent the magnitude) of the Cotton effect. For saturated ketones in which the second sphere is achiral, the position and nature of substituents in the third and outer spheres determine the Cotton effect according to an Octant (or perhaps Quadrant) Rule.

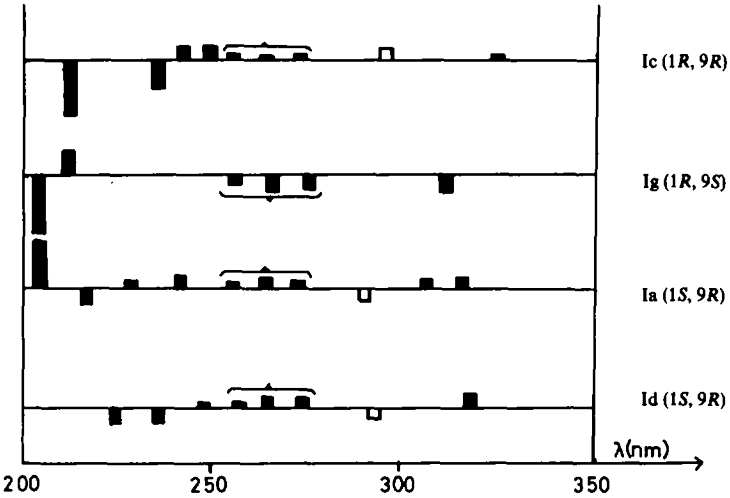


FIG. 6 Schematic diagram of partial CD bands of some lactone alkaloids (in methylcyclohexane). Meaning of bars as in Fig. 3. Origin of bands below 250 nm uncertain; black bars in this range do not mean that the band is necessarily of *P*-origin. The bracket indicates a single band with fine structure.

We now apply the concept of spheres to tetralins (IX) and to their heteroanalogues, including tetrahydroisoquinolines (X), to which class the phthalide alkaloids belong. In a tetralin or a tetrahydroisoquinoline the aromatic ring forms the first sphere, and the second (reduced) ring B represents the second sphere. From the general conception[24] that the dissymmetric sphere which is nearest to the chromophore determines the Cotton effect, one can assume that the chirality of the reduced ring in a tetralin or tetrahydroisoquinoline is chiefly responsible for the sign of the CD of the $^1L_b$ and $^1L_a$ bands.

From general symmetry considerations it is seen (cf. Schellman[32]) that for a benzene ring carrying a chiral substituent the nodal planes of the $^1L_b$ and $^1L_a$ transitions, together with the plane of the ring, determine six upper and six lower sectors. The strong dipole induced by an *ortho*-$(RO)_2$-grouping, when present, tends to superimpose a $C_{2v}$-symmetry upon the system;[32] this suggests then the application of quadrant rules[33-36] as has been proposed by Japanese groups[33-35] who have studied in detail the ORD and CD of Amaryllidaceae alkaloids. These (mainly rigid) compounds of the chiral type, whose projection (from the aromatic ring towards the piperideine ring) is as shown in Fig. 9, give a positive Cotton effect for the $^1L_b$ band, and their enantiomers a negative effect.

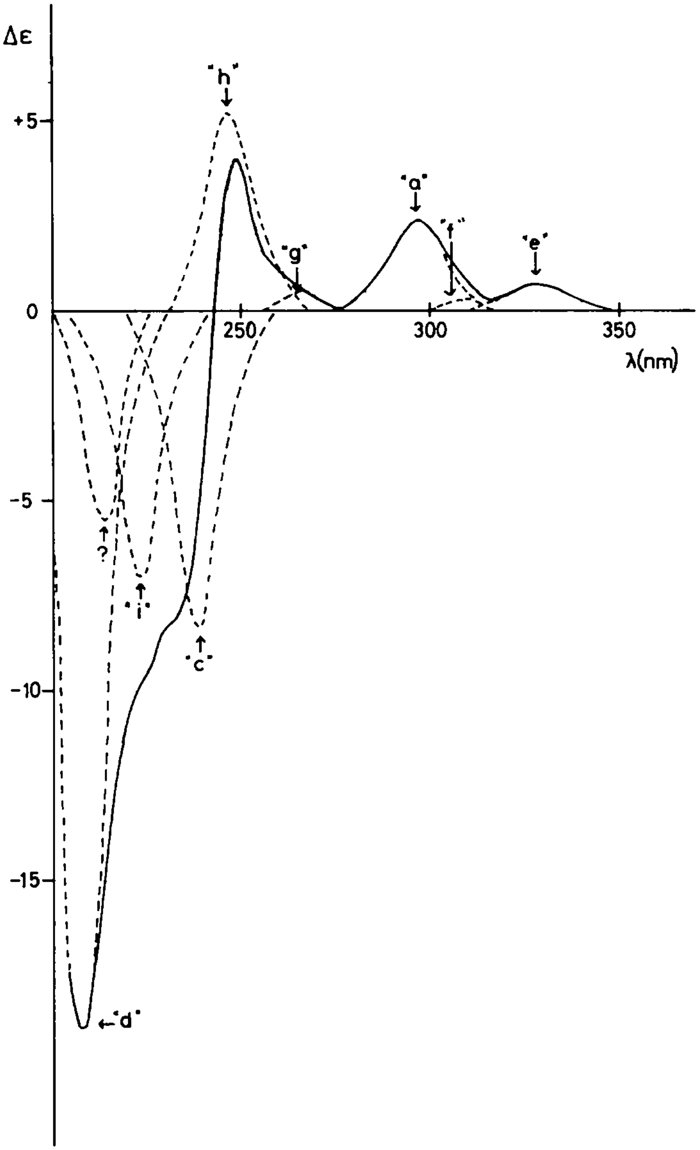


FIG. 7 CD spectrum of capnoidine (Ic) in ethanol: (———) actual curve; (– – – –) resolved bands.

The Japanese authors have rationalised these results in terms of a Quadrant Rule based on the local $C_{2v}$-symmetry of the catechol chromophore. We believe, however, that any sector rule should more properly be applied only to contributions of the third, fourth and further spheres. Furthermore we have found that the contributions of atoms (in more distant spheres) can better be rationalised by using a sector rule of $C_{6h}$-type.[37]

The Cotton effect of the $^1L_b$ band of lignans with 4-aryltetralin structure[38] follows

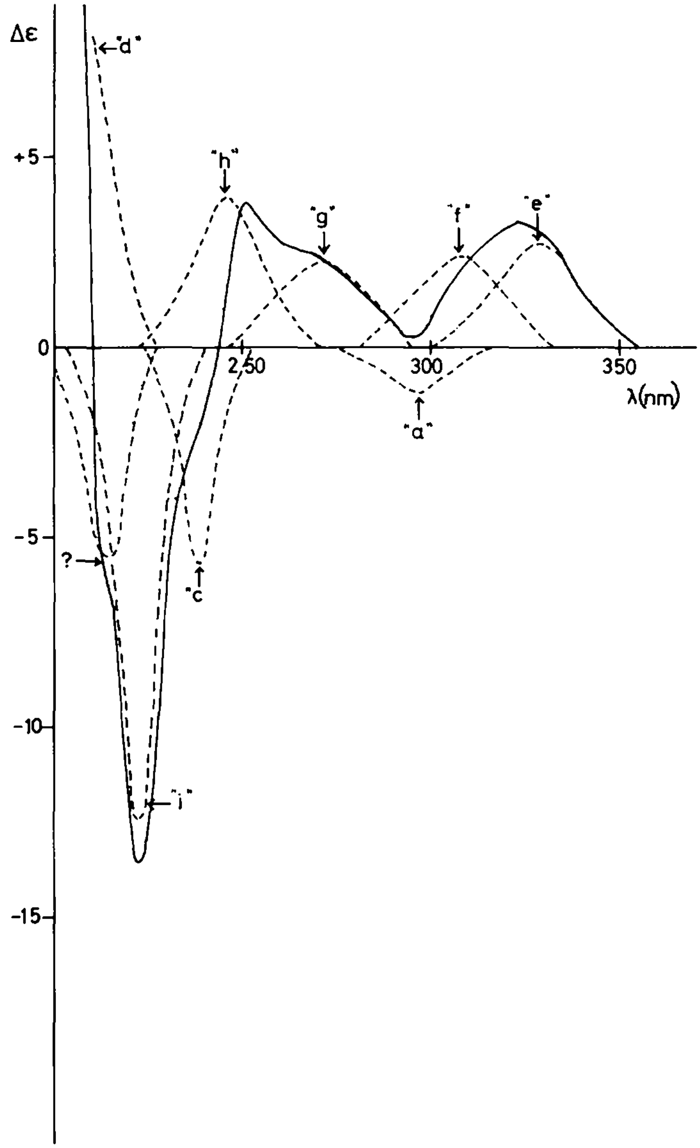


FIG. 8 CD spectrum of bicuculline (Ia) in ethanol: (———) actual curve; (- - - - -) resolved bands.

in principle a similar treatment by spheres, if one assumes that in compounds with non-rigid structures the larger substituents adopt equatorial conformations.

For tetrahydroisoquinolines[11, 14–16] the Cotton effect of the $^1L_b$ band is opposite in sign to that of the corresponding tetralins[38] with the same configuration at C-1. This fact can now be rationalised by assuming that a substituent at C-1, which preferentially adopts the quasi-equatorial conformation in tetralins, has the opposite behaviour in tetrahydroisoquinolines, and takes up the quasi-axial conformation. The apparent "anomeric effect" demonstrated by NMR in several 2-alkylsubstituted piperidine derivatives[39] is, however, due to steric interaction with the N-acyl group. All (1*R*) phthalideisoquinoline derivatives (regardless of the configuration at C-9) therefore give a projection as indicated in Fig. 9; this would be expected to lead to a positive ${}^{1}L_b$ band of the *T*-part, as is indeed the case.

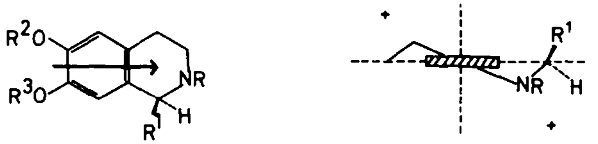


FIG. 9 Schematic projection of the two rings of a 1-axial substituted tetrahydroisoquinoline (the thick bar stands for the catechol ring) in the direction of the arrow. This chirality leads to a positive ${}^{1}L_b$ CD band.

As the ${}^{1}L_a$ band of the *T*-system cannot be identified unequivocally in the CD curves, we cannot test our assumptions for this band. The *P*-system may also be amenable to a similar treatment in principle; but again we do not attempt this at present, as the assignments for the ${}^{1}L_b$ and ${}^{1}L_a$ bands of this system are uncertain.

### *Comparison of ORD and CD curves*

The ORD curves (for examples see Figs. 10 and 11) generally follow the pattern expected from a study of the CD curves. (For this comparison, CD curves in methanol are employed, as this solvent alone was used for ORD). As is often the case the CD bands are better separated than the ORD Cotton effects, which sometimes overlap considerably. In the present series this overlapping leads fortuitously to ORD curves, some of which *appear* to be simpler than the corresponding CD curves.

The phthalideisoquinoline alkaloids give in general, three apparent ORD Cotton effects, from the signs of which the sense of the two centres of chirality may be separately determined. The first Cotton effect (335–320 nm) (cf. CD band "e") corresponds to the UV maximum at about 325 nm. (it is shifted to lower wavelengths in β-hydrastine and the narcotines). Its sign depends on the configuration at C-9, being positive for the 9*R*- and negative for the 9*S*-configuration. This Cotton effect is "echoed" by a third Cotton effect between 255 and 235 nm (cf. CD band "h"), of the same sign, and bearing the same relationship to the configuration at C-9. This Cotton effect is possibly related to the UV inflection at 235 nm. (The curves for β-hydrastine (I g) and the narcotines (I h, j) were inconsistent with the general pattern of this short wavelength Cotton effect).

In between these two effects, there is a "second" Cotton effect between 300 and 280 nm (cf. CD band "a"), corresponding to the UV maximum at about 290 nm. Its sign depends on the configuration at C-1, (positive for 1*R*; negative for 1*S*). This is entirely consistent with the observation[14, 15] that simpler 1-benzyltetrahydroisoquinolines with the *R* or *S* configurations give a negative or positive Cotton effect respectively.

Where the first (335–320 nm) and second (300–280 nm) Cotton effects are of opposite sign, the second extremum of the first Cotton effect may disappear or may appear as an inflection. This is shown in Fig. 10, which gives examples of the characteristic curves for the four possible stereoisomeric types. When the second extremum of the first Cotton

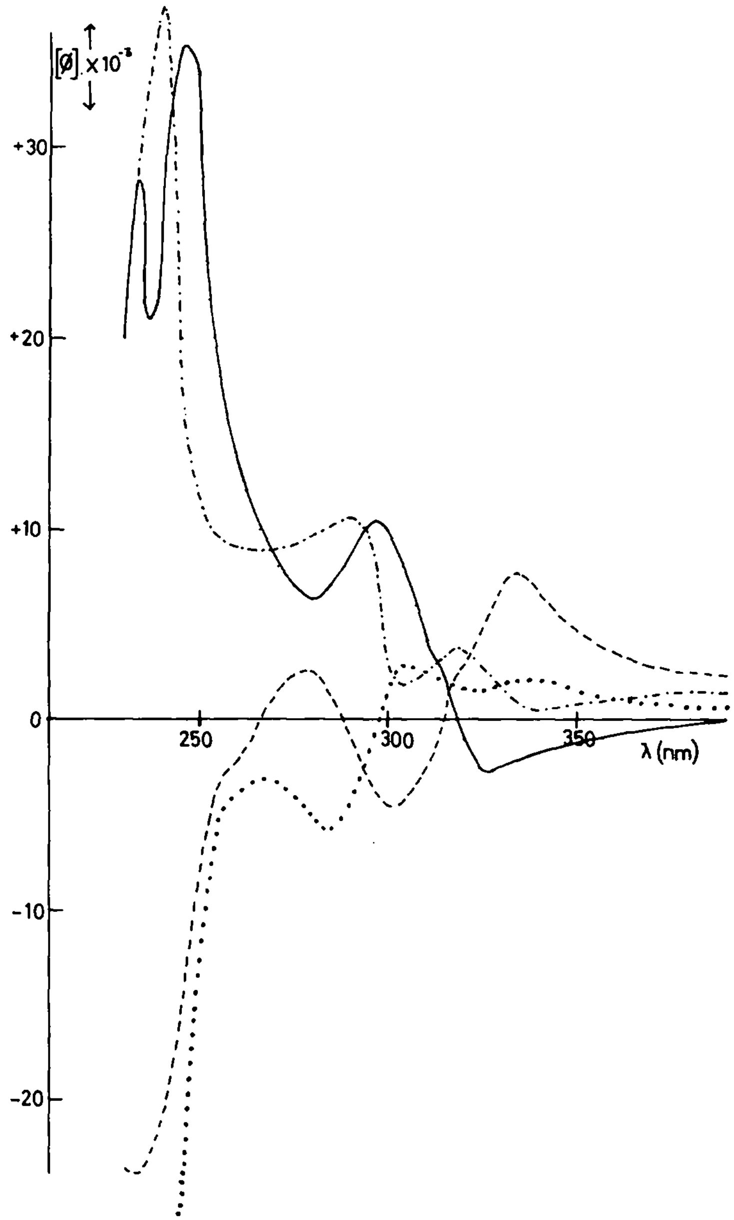


FIG. 10 ORD curves of alkaloids (I) in methanol

——————, β-Hydrastine (1*R*, 9*S*)
– – – – – –, Bicuculline (1*S*, 9*R*)
. . . . . ., Capnoidine (1*R*, 9*R*)
.–.–.–.–.–, Adlumidine (1*S*, 9*S*)

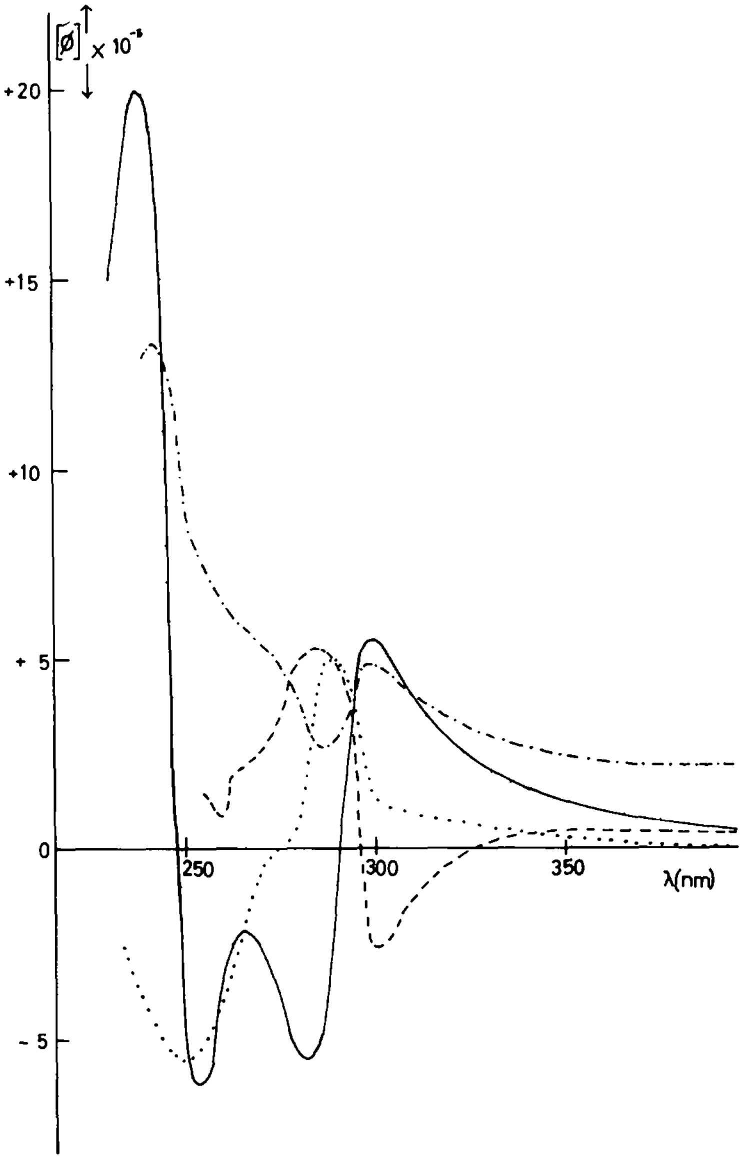


FIG. 11 ORD curves of diols (II) in methanol

———, β-Hydrastine diol (1*R*, 9*S*)
– – – – – –, Bicuculline diol (1*S*, 9*R*)
. . . . . ., Capnoidine diol (1*R*, 9*R*)
·–·–·–·–·, Adlumidine diol (1*S*, 9*S*)

effect disappears, it may give the impression that there is one single Cotton effect between 335 and 280 nm. (cf. the curves for the hydrastines and narcotines reproduced by Ohta *et al.*[3] and by Crabbè[11]).

### *The α-hydroxybenzyltetrahydroisoquinolines*

These compounds, the "diols" (II), are obtained by the reduction of the phthalide-isoquinolines with LAH, without change in configuration at the centres of chirality. They are much more flexible than the lactones and little safe interpretation is possible. Furthermore, the CD curves were measured only with the early, less sensitive Dichrographe.

TABLE 4. THIN LAYER CHROMATOGRAPHY

Phthalideisoquinoline alkaloids (I) and their α-hydroxybenzyltetrahydroisoquinoline derivatives (diols, II).
Silica gel G. Solvent systems, (*A*) benzene–ethanol (20:5) + 5 drops of $NH_4OH$; (*B*) benzene–methanol (80:20)

| Formula (I or II) | Substance | $R_f$ values Alkaloids (I) |  | Diols (II) |  |
|---|---|---|---|---|---|
|  | System | *A* | *B* | *A* | *B* |
| a | Bicuculline | 71 | 63 | 50 | 23 |
| b | (+)-Adlumidine | 74 | 80 | 45 | 22 |
| c | (−)-Capnoidine | 74 | 80 | 45 | 22 |
| d | Corlumine | 63 | 54 | 40 | 25 |
| e | Corlumidine | 46 | 36 | 37 | 21 |
| f | (+)-Adlumine | 70 | 72 | 44 | 21 |
| h | β-Hydrastine | 68 | 56 | 49 | 37 |
| g | α-Hydrastine | 71 | 63 | 45 |  |
| j | α-Narcotine | 73 | 65 | 46 | 30 |
| k | β-Narcotine | 69 | 60 | 30 | 36 |

The CD curves of the diols lack the 325 nm ("e") band which can, therefore, be definitely ascribed to the phthalide system. Furthermore, neither conjugation band nor n → π*-band is possible. Thirdly, in altering the phthalide (*P*) system to a dialkylcatechol (*D*) system, the type of the second chromophore has changed, and we cannot therefore assume the same sing pattern as was used for the (*P*) system. Many more conformations are possible and H-bonding might complicate the picture further; it is therefore impossible to attempt any fundamental interpretation of the CD curves.

It is reasonable to suggest that the tetrahydroisoquinoline nucleus (*T* system) "sees" chiefly the chirality at C-1, and the dialkylcatechol (*D* system) "sees" chiefly the chirality at C-9 (cf XI). Since the absorption bands of the two systems are more or less coincident, the two sets of Cotton effects may be (more or less) additive.

The results of the CD measurements can be explained, if one assumes a negative sign for the $^1L_b$ band of the *D*-system in the 9*R*-configuration. For the $^1L_a$ band no interpretation is possible. Adlumidine diol gives a curve of enantiomeric type to that of capnoidine diol, although we were unable to measure the first compound to short wavelengths.

In the ORD curves (cf. Fig. 11) only one Cotton effect gives stereochemical information, *viz*:- that between 300 and 285 nm, corresponding to the UV maximum at 290 nm. The sign is governed chiefly by the configuration at C-9 (negative for 9*R*-; positive for 9*S*-). However, its amplitude is affected to a lesser extent by the configuration at C-1, as would be expected, since the 1-benzyltetrahydroisoquinolines (*T* system) give a Cotton effect in this region. If the contribution of the *T*-system to the Cotton effect in the diols (II) is positive and negative for 1*R* and 1*S*-configurations respectively (as in the simpler compounds (III)), then we can rationalise the relative amplitudes of the diastereoisomeric diols (II), as follows:

| Configuration | Contributions to Cotton Effect | | Total Cotton Effect (ca. 290 nm) | | |
|---|---|---|---|---|---|
| | At C-9 | At C-1 | Expected | Found ORD (*a*) | Found CD (Δε) |
| I*R*, 9*R* | + | − − | − | −38 | −0·7 |
| 1*S*, 9*S* | − | + + | + | +22 | +0·8 |
| 1*R*, 9*S* | + | + + | + + + | +112 | ... |
| 1*S*, 9*R* | − | − − | − − − | −89, −66 | −2·2 |

The results might be summarised in another way by stating that *erythro* and *threo* configurations give large and small Cotton effects respectively. The presence of a considerable Cotton effect due to asymmetry at C-9 implies considerably restricted rotation of the aromatic ring attached to it.

The narcotine diols (IIh, j) do not fit the general pattern, presumably on account of the extra OMe group at C-8.

## EXPERIMENTAL

The alkaloids and their diols are the same as those described earlier.[2] A revision of the measurements of the compounds given below was carried out.

### *General methods*

*Dissociation constants.* These were recorded in methylcellosolve (80%) using an automatic registration Titrator Model TTT1 c, manufactured by Radiometer Ltd., Denmark, and the titration was carried out with 0·1N HCl solutions.

*Thin-layer chromatography.* Silica gel G (5–30 μ mesh) was used. For solvent systems, see Table 4.

*UV spectra.* These were measured in Bonn in MeOH, EtOH, MeCN, N HCl, and in some cases in methylcyclohexane, using a Unicam SP-700 or Cary 14 spectrophotometer.

*Optical rotatory dispersion.* ORD measurements were made at ca. 20° in MeOH, using the Bellingham and Stanley/Bendix-Ericsson automatic spectropolarimeter "Polarmatic 62". Concentrations were approximately $3 \times 10^{-4}$M for the phthalideisoquinolines and $2 \times 10^{-4}$M for the α-hydroxybenzyltetrahydroisoquinolines, using a 1·0 cm cell. Details of the principal extrema are given in Tables 1 and 2.

*Circular dichroism.* CD measurements were made at 20° in different solvents with the Roussel–Jouan Dichrographes (earlier model and new "CD 185") at a concentration of approximately $1–3 \times 10^{-3}$M in cells of 2·00, 1·00, 0·50, 0·20, 0·10 or 0·01 cm path length. Details of the CD curves are given in Tables 1 and 2.

### *New data characteristic of individual compounds.*

Solvents indicated are those used for recrystallization. Specific rotations for the *D*-line were measured in $CHCl_3$ (*c*, usually about 0·7–0·8); experimental error, ±3°.

Bicuculline,[40,41] from EtOAc, m.p. 236–238°; $[\alpha]_D^{22}$ −134·7°; p*Ka* 4·84.

Bicuculline diol, from EtOAc, m.p. 152–155°; $[\alpha]_D^{22}$, −8°.

(+)-Adlumidine, from EtOAc, m.p. 233–235°; $[\alpha]_D^{22}$ −104°; p*Ka*, 4·27.

(+)-Adlumidine diol could not be crystallized from any common solvent. Samples for the determination of the optical rotation were dried for 4 hr at 0·01 Torr; $[\alpha]_D^{22}$ +11°.

(−)-Capnoidine, from EtOAc, m.p. 233–235°; $[\alpha]_D^{22}$ −105°; p*Ka*, 4·24.

(−)-Capnoidine diol could not be crystallized from any common solvent; $[\alpha]_D^{22}$ −10°.

(±)-Capnoidine, from EtOAc, m.p. 203–205°; p*Ka* 4·22.

(−)-β-Hydrastine from EtOAc, m.p. 133–135°, $[\alpha]_D^{22}$ −61°. The corresponding diol, from EtOAc, m.p. 145–146°; $[\alpha]_D^{22}$ +19°; p*Ka*, 6·61.

(−)-β-Narcotine[42] from EtOAc, m.p. 176–177°; $[\alpha]_D^{22}$ −195°; p*Ka*, 4·70.

β-Narcotine diol from EtOAc, m.p. 62–64°; $[\alpha]_D^{22}$ −63°; p*Ka*, 7·06. (TLC showed that the compound contained traces of α-narcotine diol.)

(−)-α-Hydrastine (stylophylline[43]) literature m.p., 160–161°.

### *Preparation and properties of reference compounds*

*Resolution of ethyl* 1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinolyl*-1-*acetate* (VI). The racemate (590 mg) and (+)-tartaric acid (332 mg) were dissolved in the minimum amount of hot acetone; after cooling, the precipitates salt was crystallized four times from the same solvent. The final product was dissolved in water, KOH was added, and the base was isolated in the usual way by extraction with $CHCl_3$, giving the (−)-isomer (63·4 mg; $[\alpha]_D^{20}$ −30·6°).

(−)-(VI); CD (λ (nm), and Δε in parentheses).

Dioxan: 285 (−1·16), 240 (+1·57).

MeOH: 283 (−0·70), 250 (0), 231 (−3·17).

EtOH: 285 (−0·61), 247 (+0·21), 232 (−2·14).

i-PrOH: (early Dichrographe) 281 (−1·06), 242 (+0·71), 235 (0).

1N HCl: 282 (−0·55), 230 (−3·87).

6,7-*Dimethoxy*-3-N,N-*dimethylaminomethylphthalide*, 3-N,N-*dimethylaminomethylmeconine* (VII). The corresponding primary amine, obtained according to the literature[17] (5·26 g) was dissolved in 95% formic acid (5·5 g), and 35% aqueous formaldehyde soln. (4·4 g) was added with stirring. After heating for 10 hr to 100°, water (20 ml) and conc. HCl (1 ml) were added, and the resulting soln. was evaporated *in vacuo*. The residue was dissolved in aqueous ammonia and extracted six times with $CHCl_3$. After washing with water and drying with $Na_2SO_4$, the $CHCl_3$ was evaporated *in vacuo*, giving a brown oil (5·35 g) which slowly crystallized. For purification it was chromatographed on silica gel (65 g), and the eluate crystallized by slow evaporation of a $CHCl_3$ soln. m.p. 61·5–62°. (Found: C, 61·76; H, 7·00; N, 5·95. $C_{13}H_{17}NO_4$ requires: C, 62·14; H, 6·82; N, 5·57%).

*Resolution*: (a) The racemate (767 mg) in acetone (25 ml) was treated with (+)-dibenzoyltartaric acid (1·142 g) in acetone (25 ml). After warming slightly light petroleum was added, and the salt crystallized on cooling. After four crystallizations the base was isolated in the usual way; m.p. 70·5–71·5°; $[\alpha]_D^{20}$ +36·5°.

(b) The racemate (762 mg) in EtOAc (100 ml) was treated with a soln of (−)-malic acid (414 mg) in EtOAc (85 ml). The salt separated as an oil, which later solidified; it was crystallized from MeOH (25 ml), and after two further crystallizations the base was isolated in the usual way; m.p. 72–73°; $[\alpha]_D^{20}$ −37·8°.

*Compound* VII. UV absorption (λ (nm) and $\varepsilon_{max}$ in parentheses). Dioxan: 288 (3700), 283 (3700), 230i (12,500). MeOH: 282 (3900), 222i (8600), 202 (40,780, end absorption).

*Compound* (+)-VII. CD (λ (nm) and Δε in parentheses).

Dioxan†: 312 (−1·04), 263 (−0·67), 230 (+5·29!);

MeOH: 312 (−0·63), 255 (−0·72), 230 (+3·5!);

EtOH: 315 (−0·27), 255 (−0·71), 221 (+7·8).

*Compound* (−)-VII. CD Dioxan†: 305 (+0·46), 265 (+0·60), 230 (−3·6); EtOH: 315 (+0·29), 255 (+0·75), 220 (−8·4).

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† Values in dioxan with early Dichrographe; less accurate.

(S)-(−)-*Butylphthalide* (ent-VIII; R = Bu), from Prof. Mitsuhashi, CD (λ (nm) and Δε in parentheses.)
EtOH: 281 (+0·07), 268i (+0·12), 254 (+0·26), about 255 (+0·4); acetonitrile 269i (+0·12), 261i (+0·26), 256 (+0·32), about 222 (+0·6); i-octane: 284 (−0·13), 280 (−0·16), 268i (+0·17), 262 (+0·39), 256 (+0·41), 249i (+0·27), about 220 (+0·7).

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