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CORYNANTHEIDINE-TYPE ALKALOIDS—II

ABSOLUTE CONFIGURATION OF MITRAGYNINE, SPECIOCILIATINE, MITRACILIATINE AND SPECIOGYNINE

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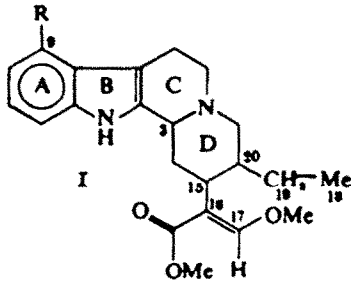
Abstract—The absolute configuration of mitragynine (*allo*), speciociliatine (*epiallo*), mitraciliatine (*pseudo*), and speciogynine (*normal*) has been determined from IR, NMR, ORD and CD data; all have the C15 hydrogen α. Moreover, the preferred conformation of each configuration has been established. The absolute configuration of any ring substituted or unsubstituted corynantheidine-type alkaloid of unknown configuration can be determined by use of the physical criteria presented.

IN THIS paper the absolute configuration of four *Mitragyna* alkaloids is established utilizing the physical criteria presented in the preceding paper.[1] These criteria are first applied to two compounds (I, R = H) of known absolute configuration, (corynantheidine and dihydrocorynantheine) and then to four diastereoisomers (I, R = —OMe) one of which, mitragynine, is of known relative configuration.



I

Corynantheidine (I, R = H, *Allo*, C15 Hα)

The absolute configuration of corynantheidine has been established[2-4] as C3H α, C15 Hα and C20 Hα (*allo*). A *cis* geometry (methoxy and carbomethoxy groups) has been suggested[5] for the C16-C17 double bond because of the observation of a chemical shift difference ($\Delta\delta$) between the C17 vinyl proton signal of corynantheidine (7·32 δ)

* To whom inquiries should be directed.

[1] W. F. Trager, C. M. Lee and A. H. Beckett, *Tetrahedron* **23**, 365 (1967).

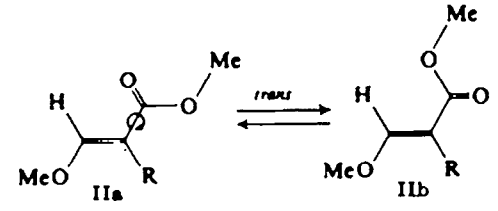
[2] E. E. van Tamelen, P. E. Aldrich and T. J. Katz, *Chem. & Ind.* 793 (1956).

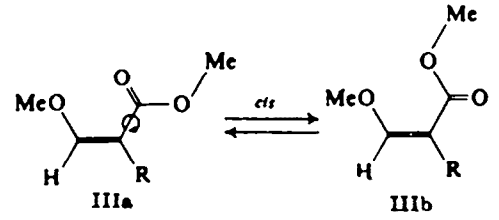
[3] M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Brinji and E. Wenkert, *J. Amer. Chem. Soc.* **84**, 622 (1962).

[4] J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim and B. Douglas, *Tetrahedron Letters* No. 39, 9457 (1965).

[5] E. Wenkert, Borje Wickberg and C. Leicht, *Tetrahedron Letters* No. 22, 822 (1961).

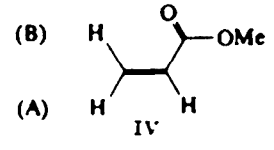
and the vinyl proton signal of ajmalicine (7·54 δ) where the vinyl proton must be *cis* to the carbomethoxy group. However, Weisbach *et al.*[4] pointed out that the C17 vinyl H signal of mitragynine [*allo* configuration[6] (I, R = OCH_3) with known *trans* double bond geometry shown by X-ray crystallography[7]] was identical to *their* observed chemical shift value for the corresponding proton of corynantheidine (7·45 δ) and suggested that corynantheidine be reassigned the *trans* double bond geometry (methoxy/carbomethoxy).





R = Rings A–D of I

The NMR data (Table 1) for the C17 olefinic proton of corynantheidine-type compounds (I, R = H or —OCH_3) may be used to allocate the geometry about the C16–C17 double bond. In the *trans* configuration the olefinic proton will be deshielded in the two planar rotomers (IIa–IIb). In IIa, deshielding arises from the proximity of the carbonyl group[8] while in IIb the deshielding results from the oxygen[9] of the methoxy (assuming effects of methoxy are similar to hydroxy). In both *cis* rotomers (IIIa–IIIb) this type of deshielding is not possible. Therefore compounds with *trans* double bond geometry would be expected to have the olefinic proton signal significantly *downfield* relative to the corresponding signal in the *cis* compounds.



Support for the above may be derived from consideration of the NMR spectrum

[6] B. S. Joshi, Raymond Hamet and W. I. Taylor, *Chem & Ind.* 573 (1963).
[7] D. E. Zacharias, R. D. Rosenstein and G. A. Jeffrey, *Acta. Cryst.* **18**, 1039 (1965).
[8] L. M. Jackman *Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry* p. 119. Pergamon, New York (1959).
[9] A. C. Huitric, J. B. Carr and W. F. Trager, *J. Pharm. Sci.* **55**, 211 (1966).

of methyl acrylate (IV);[10] the chemical shift of proton (A) which is *trans* to the ester group is at higher field (5·82 δ) than proton (B) which is *cis* to the ester group (6·38 δ). This difference of 0·56 ppm corresponds to about 34 cps at 60 mc. Thus the vinyl proton signal in the *trans* compound II would be expected to occur about 30 c/s downfield from that of the *cis* compound III. Since the chemical shift spread for corynantheidine alkaloids (Table 1) is only about 8 c/s, it would appear that all these compounds have the same double bond geometry as mitragynine in which the *trans* geometry has been established.[7]

The slight chemical shift differences observed in the olefinic proton signal (Table 1) are probably related to the relative configuration of the C15 and C20 substituents in

TABLE 1. NMR C17 OLEFINIC SIGNALS FOR CORYNANTHEIDINE-TYPE ALKALOIDS

C15 H_{ax}, C20 H_{eq}	Our data*	Weisbach[4]†	Wenkert[6]*
Mitragynine	7·45	7·45	—
Speciociliatine	7·43	—	—
Corynantheidine	7·47	7·45	7·32
C15 H_{ax}, C20 H_{ax}			
Speciogynine	7·37	—	—
Mitraciliatine	7·33	—	—
Dihydrocorynantheine	7·40	7·42	—

* δ values, ppm from TMS in $CDCl_3$.
† δ values, ppm from TMS in deuteroacetone.

these compounds. Corynantheidine and those compounds later shown to have the C15 H *axial* and the C20 H *equatorial* (mitragynine and speciociliatine) have olefinic signals appearing at slightly lower field (7·43–47 δ) than that of dihydrocorynantheine and those compounds later shown to have both the C15 H and C20 H *axial* (speciogynine and mitraciliatine) (7·33–40 δ).

The infrared spectrum of corynantheidine (KCl disc) has bands at 2753 and 2798 cm^{-1} in addition to the strong CH absorption at 2955 cm^{-1}, indicative of a *trans* C3H junction.[12,1] The *trans* C3H configuration is further confirmed by the absence of a one-proton C3H multiplet in the NMR below 3·8 ppm.[11] The methyl triplet signal is relatively well resolved as indicated by its symmetrical appearance at 100 mc (Fig. 1a). These data for a compound of *known allo* configuration fulfil only the requirements (Table 2) for the postulated preferred conformation CI. (Fig. 2).

The ORD/CD curves (Fig. 3a, dioxane) show multiple positive Cotton Effects (CE) associated with the UV absorption between 270–300 mμ. Since corynantheidine has the C15 Hα absolute configuration, any corynantheidine-type compound of *allo* configuration showing positive CE at 270–300 mμ must also have the C15 Hα.

[10] N. S. Bhacca, L. F. Johnson and J. N. Shoolery, *NMR Spectra Catalog* Vol. I; No. 64 (1962).
[11] M. Uskokovic, H. Bruderer, C. von Planta, T. Williams and A. Brossi, *J. Amer. Chem. Soc.* **86**, 3364 (1964).
[12] E. Wenkert and D. K. Roychaudhuri, *J. Amer. Chem. Soc.* **78**, 6417 (1956).

Dihydrocorynantheine (I, R = H, *Normal*, C15 Hα)

The absolute configuration of dihydrocorynantheine[3,4,13] has been established as C3Hα, C15 Hα, C20 Hβ placing the compound in the *normal* configuration. Dihydrocorynantheine has IR bands at 2750, 2805 and 2850 cm^{-1}, in addition to the strong

Table 2. Prediction of physical consequences of the conformations of corynantheidine-type alkaloids I

Configuration	C3 H *trans* IR bands	C3 H *cis* NMR multiplet below 3·8 δ-Bandwidth		C 18 NMR triplet resolution	ORD/CD
Normal					
• AI	+	−	—	poor	A
AII	−	+	14 c/s	poor	‡‡
AIII	−	+	8 c/s	fair	‡‡
Pseudo					
• BI	−	+	8 c/s	poor	B
BII	−	+	14 c/s	poor	‡‡
BIII	+	−	—	fair	‡‡
Allo					
• CI	+	−	—	fair	A
CII	−	+	14 c/s	poor	‡‡
CIII	−	+	8 c/s	poor	‡‡
Epiallo					
• DI	−	+	8 c/s	fair	B
DII	−	+	14 c/s	poor	‡‡
DIII	−	−	—	poor	‡‡

• Preferred conformation.
+ Present.
− Not present.
A = + or − (B is the opposite sign).
‡‡ Not predicted.

2945 cm^{-1} CH absorption, so that the configuration of the C3H relative to the nitrogen lone pair is *trans*. This is also confirmed by the absence of a one-proton C3H multiplet below 3·8 ppm in the NMR spectrum. The NMR triplet signal of the methyl group is poorly resolved as indicated by its unsymmetrical appearance at 100 mc (Fig. 1d) and as postulated for the preferred conformation of a compound of *normal* configuration, AI (Fig. 2). The ORD/CD curves of dihydrocorynantheine (Fig. 3d) show positive CE between 270–300 mμ. Comparison of the ORD/CD curves of dihydrocorynantheine and corynantheidine indicate that inversion of C20 does not affect the sign of the CE at 270–300 mμ.

These data for dihydrocorynantheine of known *normal* configuration agree only with those of the predicted preferred conformation of that configuration (AI, Table 2). The ORD/CD data show that any compound of corynantheidine-type structure of *normal* configuration giving positive CE (270–300 mμ) will have the C15 Hα.

[13] E. Wenkert and N. V. Brinji, *J. Amer. Chem. Soc.* **81**, 1474 (1959).

Mitragynine (I, R = OMe, *Allo*, C15 Hα)

Physical evidence[6,14] and X-ray crystallography[7] have shown that mitragynine is a compound of *allo* configuration with *trans* double bond geometry.[7] As expected, the IR spectrum shows C3H *trans* bands at 2750, 2800 and 2870 cm^{-1} in addition to the strong 2950 cm^{-1} CH absorption; no C3H NMR multiplet appears below 3·8 ppm. The methyl group is relatively well resolved in the NMR (Fig. 1b) confirming that the preferred conformation CI is present in mitragynine as well as in corynantheidine. The ORD/CD curves of mitragynine (Fig. 3b) are very similar to those of corynantheidine (Fig. 3a) with both exhibiting positive CE at 270–300 mμ. Thus mitragynine must have the same absolute configuration as corynantheidine: C3 Hα, C15 Hα, C20 Hα.

Application of physical analysis (Table 2) to corynantheidine-type compounds of unknown configuration

We are fortunate in having four compounds of the same chemical constitution (I, R = —OMe: mitragynine, speciogynine, speciociliatine and mitraciliatine) from the *Mitragyna* species but differing in their relative configurations.* The NMR data (Table 1) indicate *trans* double bond geometry in all these compounds. Since the configuration of mitragynine is known to be *allo*, the remaining three alkaloids must each fall into only one of the remaining three configurations *viz. normal*, *pseudo* or *epiallo*. IR and NMR measurements (Table 2) on these compounds establish relative configuration while ORD/CD measurements establish the absolute configuration of each alkaloid.

Speciociliatine (I, R = OMe, *Epiallo*, C15 Hα)

Speciociliatine[15,16] shows only one small IR band (2856 cm^{-1}) before the major 2930 cm^{-1} CH stretch; moreover, a one-proton multiplet at about 4·1 ppm (band width approximately 9–10 c/s) is observed in the NMR.[16] Both these data indicate that the hydrogen at C3 in speciociliatine is *cis* to the nitrogen lone pair.[1] Resolution of the NMR methyl triplet (Fig. 1c) shows greater similarity to that of corynantheidine (symmetrical) than to that of dihydrocorynantheine (unsymmetrical) (Fig. 1d). This information fits only the criteria for a compound of *normal* configuration in conformation AIII or a compound of *epiallo* configuration in conformation DI. Since the preferred conformation of a *normal* compound (dihydrocorynantheine) has been shown to be the expected preferred conformation AI, and not the very hindered AIII,[1] speciociliatine can only have the *epiallo* configuration and exists primarily in conformation DI (Fig. 2).

The sign of the first CE (270–300 mμ) of the *epiallo* or *pseudo* compound was expected to be opposite to that of the *normal* or *allo* compound on the assumption that all C15 hydrogens were α and the configuration at C3 governs the sign of the CE.[1] To establish the absolute configuration of speciociliatine and to confirm the above assumptions, reference is now made to reserpine (V), a compound of known absolute

* We wish to thank Dr. J. D. Phillipson for providing speciogynine and speciociliatine.

[14] A. H. Beckett, E. J. Shellard and A. N. Tackie, *Planta Medica* **13**, 241 (1965).

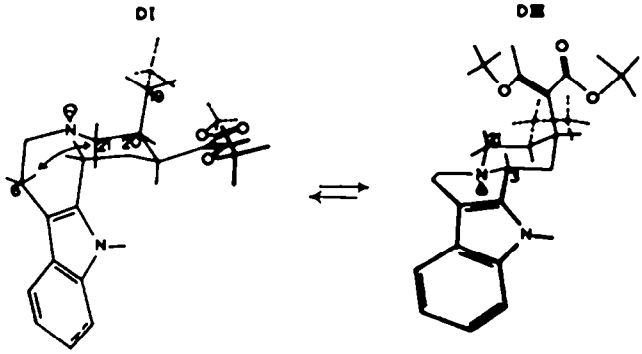
[15] A. H. Beckett, E. J. Shellard, J. D. Phillipson and C. M. Lee, *J. Pharm. Pharmacol.* **17**, 753 (1965).

[16] A. H. Beckett, E. J. Shellard, J. D. Phillipson and C. M. Lee, *Planta Medica* **14**, 277 (1966).

epiallo geometry[17-19] (C3 Hβ, C15 Hα, C20 Hα), which gives negative CE (Fig. 4). Since the sign of the CE is independent of the configuration of asymmetric centres relatively far removed from the perturbed chromophore, viz. indole ring (e.g. C20 in corynantheidine and dihydrocorynantheine, Fig. 3) then the sign of the CE for reserpine must be independent of the configuration of the relatively far removed centres (C16, C17 and C18). Hence, speciociliatine, which also exhibits negative CE (Fig. 3c) and has been shown to be an *epiallo* compound (i.e. C3 Hβ, C15 Hα, C20 Hα, or C3 Hα, C15 Hβ, C20 Hβ), must have an absolute stereochemistry similar to that of reserpine (i.e. C3 Hβ, C15 Hα, C20 Hα) because of the similarity of its CE to those of reserpine.

Conformational mobility in epiallo compounds

Epiallo compounds of corynantheidine-type might exist as an equilibrium mixture between DI and DIII depending on the $-\Delta G^\circ$ of the *axial* ester–enol-ether link in DIII.[1]



Previously, Rosen and Shoolery[20] showed by IR and NMR data that certain *epiallo* reserpine alkaloids can exist in conformations analogous to either DI or DIII depending on the relative orientation of the ring E substituents. Reserpine[20] V exists in a conformation analogous to DI as the ring E substituents are in the favoured tri-*equatorial* orientation. On the other hand, methyl neoreserpate[20] VI, also *epiallo*, exists in a conformation analogous to DIII since this conformation accomodates two ring E substituents in *equatorial* orientations.

The NMR signal of the *cis* C3H multiplet appears at about 4·45 ppm in reserpine[20] (*epiallo*) and mitraciliatine (*pseudo*),* compounds which are expected to exist *essentially* in a conformation (DI and BI) where the C3H is *equatorial* and *cis* to the nitrogen

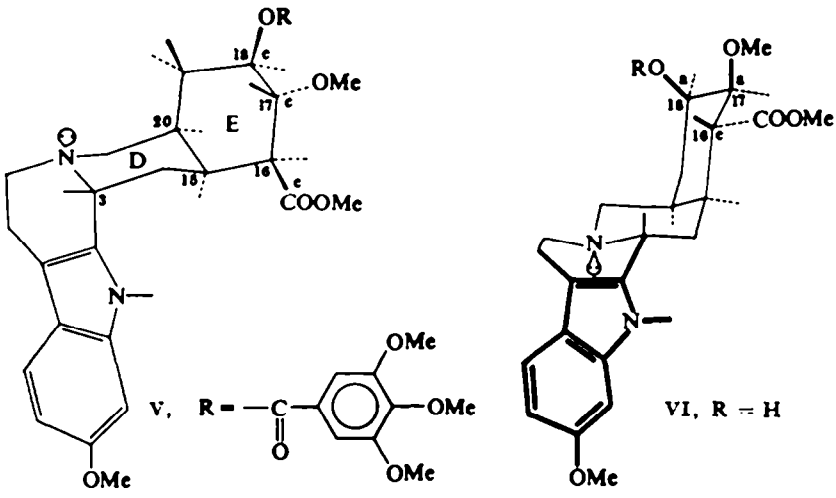
* See following discussion.

[17] P. A. Diassi, F. L. Weisenborn, C. M. Dylion and O. Wintersteiner, *J. Amer. Chem. Soc.* **77**, 2028 (1955).

[18] P. E. Aldrich, P. A. Diassi, D. F. Dickel, C. M. Dylion, P. D. Hance, C. F. Juebner, B. Korzun, M. E. Kuehne, L. H. Liu, H. B. MacPhillamy, E. W. Robb, D. K. Roychaudhuri, E. Schlittler, A. F. St. Andre, E. E. van Tamelem, F. L. Weisenborn, E. Wenkert and O. Wintersteiner, *J. Amer. Chem. Soc.* **81**, 2481 (1959).

[19] Y. Ban and O. Yonemitsu, *Chem. & Ind.* 948 (1961), *Tetrahedron* **20**, 2877 (1964).

[20] W. E. Rosen and J. N. Shoolery, *J. Amer. Chem. Soc.* **83**, 481 (1961).



lone pair. The chemical shift of the C3H multiplet, 4·12 ppm, of speciociliatine indicates that the alkaloid does not exist entirely in conformation DI as its position is 0·3 ppm upfield from that of the above mentioned alkaloids. The presence of some proportion of conformation DIII, where no C3H downfield multiplet is expected, is therefore indicated.

In a mobile *epiallo* system where more than one conformation is possible (e.g. DI $\rightleftharpoons$ DIII), the chemical shift signal (δ) of any given proton will be the weighted time average of its chemical shift in pure DI (δ_{eq}) where the C3H is *equatorial* and in pure DIII (δ_{ax}) where C3H is *axial*, provided conformational interchange is rapid. A rough approximation of the percentage of DIII present is then given by the equation:[21,22] % of DIII $= 100(\delta_{eq} - \delta_x)/(\delta_{eq} - \delta_{ax})$ where δ_x is the observed δ of the C3H, δ_{eq} is taken to be 4·45 ppm and $\delta_{eq} - \delta_{ax}$ is taken as approximately 1·3 ppm.* This calculation suggests that roughly 25% of speciociliatine exists in the *trans* C3H conformation DIII with the majority (75%) in the *cis* conformation DI, corresponding to an energy difference between DI and DIII of about 0·65 kcal/mole[24] at 25°.

* As pointed out above the δ_{eq} (DI) of the C3H is 4·45 ppm; on the other hand, corynantheidine and dihydrocorynantheine (in conformations analogous to DIII for the C3H) have their lowest downfield aliphatic proton multiplets occuring at about 3·2 ppm. Therefore $\delta_{eq} - \delta_{ax}$ must be at least 1·3 ppm. Evidence that δ_{ax} occurs in the region of 3·2 ppm can be derived from the following. Comparison of the δ_{eq}, 4·45 ppm, with the observed δ, 2·80 ppm, for the equatorial hydrogens adjacent to the nitrogen in quinolizidine[23] at C4 and C6 shows a difference of 1·65 ppm which must arise from deshielding due to the indole ring. Moreover, this deshielding of the C3H will be independent of the configuration of the C3H [*axial* (DIII) or *equatorial* (DI)] as the relative orientation of the indole ring to the C3H is constant in both DIII and DI. Addition of this deshielding effect of 1·65 ppm to the observed δ of the *axial* bridgehead hydrogen of quinolizidine i.e. 1·8 − 1·0 ppm,[23] yields an expected δ of 3·45 − 2·65 ppm for the C3H in conformation DIII.

[21] E. L. Eliel, *Chem. & Ind.* 568 (1959).
[22] N. C. Franklin and H. Feltkamp, *Angew. Chem.* (Int. Ed.) **4**, 774 (1965).
[23] F. Bohlmann, D. Schumann and H. Schulz, *Tetrahedron Letters* No. 3, 173 (1965).
[24] E. L. Eliel, *Stereochemistry of Carbon Compounds* p. 207 and back cover. McGraw-Hill, New York (1962).

The bandwidth of the C3H multiplet should be indicative of the position of equilibrium in *epiallo* compounds. Practically, this information is less useful than that derived from chemical shift differences due to the difficulty in accurately measuring the bandwidth and the inherently small difference expected, (6 c/s) between the bandwidth of pure DI (~8 c/s, J_{ae}, J_{ee}) and that of pure DIII (~14 c/s, J_{aa}, J_{ee}).

Mitraciliatine (I, R = OMe, *Pseudo*, C15 Hα)

No CH *trans* bands are found in the IR spectrum of mitraciliatine[35] but there is a one-proton downfield NMR multiplet (ca 4·45 ppm, bandwidth ca. 8 c/s); resolution of the methyl triplet in the NMR is poor (Fig. 1f). Thus all data indicate that mitraciliatine has the *pseudo* configuration and exists essentially in conformation BI (Fig. 2).

The ORD/CD of mitraciliatine (Fig. 3f) shows negative CE between 270–300 mμ and since it was shown above that the absolute stereochemistry at C3 governs the sign of the CE around 290 mμ, mitraciliatine must have the same absolute configuration at C3 as reserpine and speciociliatine and therefore has the absolute configuration: C3β, C15α and C20β.

It was demonstrated that the chemical shift position of the *cis* C3H multiplet in mitraciliatine is about 4·5 ppm while that of speciociliatine is about 4·1 ppm. It would therefore appear that the *position* of the C3H multiplet can be used as another criteria for distinguishing between *pseudo* and *epiallo* configurations in alkaloids of corynantheidine-type (Table 3).

TABLE 3. PHYSICAL CONSEQUENCES OF THE PREFERRED CONFORMATIONS OF CORYNANTHEIDINE-TYPE ALKALOIDS I

Configuration	IR Bands	*cis* C3H NMR Multiplet	Bandwidth	CH_3 Triplet Resonance	Sign ORD/CD (C15 Hα)[a]
Normal AI	+	—	—	unsymmetrical[c]	positive
Pseudo BI	—	ca 4·5 ppm	8 c/s	unsymmetrical[c]	negative
Allo CI	+	—	—	symmetrical[b]	positive
Epiallo DI/DIII	—	ca 4·1 ppm	10 c/s	symmetrical[b]	negative

[a] At 270–300 mμ (If the configuration of C15 H is β, the signs will be reversed).

[c] See Fig. 1d.

[b] See Fig. 1a.

Speciogynine (I, R = OMe, *Normal*, C15 Hα)

IR bands at 2740, 2808 and 2850 cm^{-1} and lack of a C3H downfield NMR multiplet establish a *trans* C3H configuration for speciogynine.[15,16] The methyl triplet signal in the NMR is poorly resolved like that of dihydrocorynantheidine (Fig. 1e). The only configuration remaining is *normal* and the above data fit only the criteria of the preferred conformation AI (Fig. 2). Speciogynine shows positive ORD/CD CE about 270–300 mμ (Fig. 3e) similar to those of dihydrocorynantheidine and must therefore have the C15 Hα.

The present application of the arguments outlined in the first paper[1] indicates that

[35] A. H. Beckett and A. N. Tackie, *J. Pharm. & Pharmacol. Suppl.* 15, 166T, 267T (1963) and unpublished data.

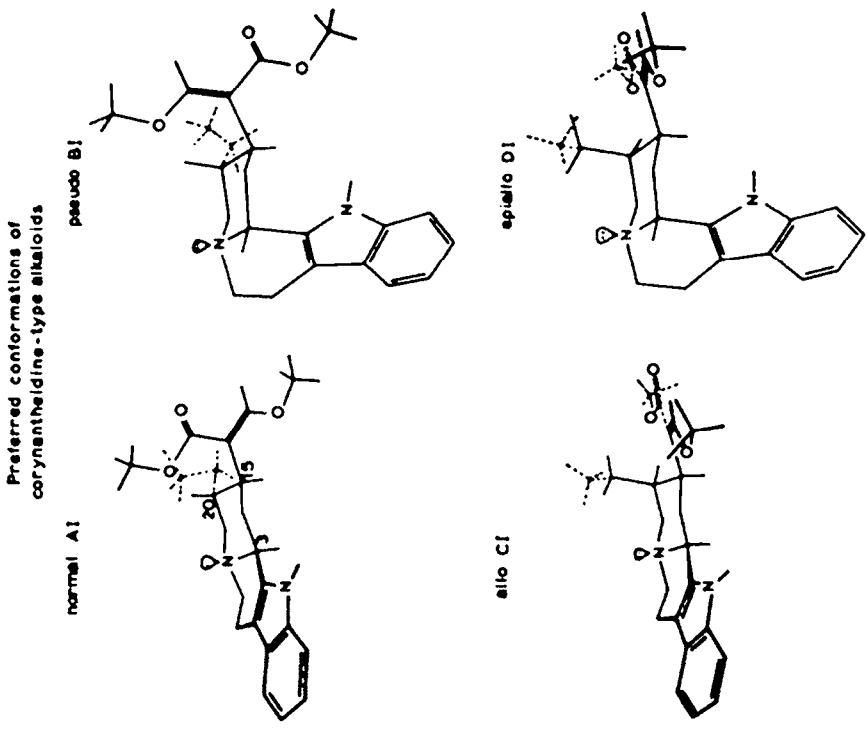


Fig 2. (as shown on figure)

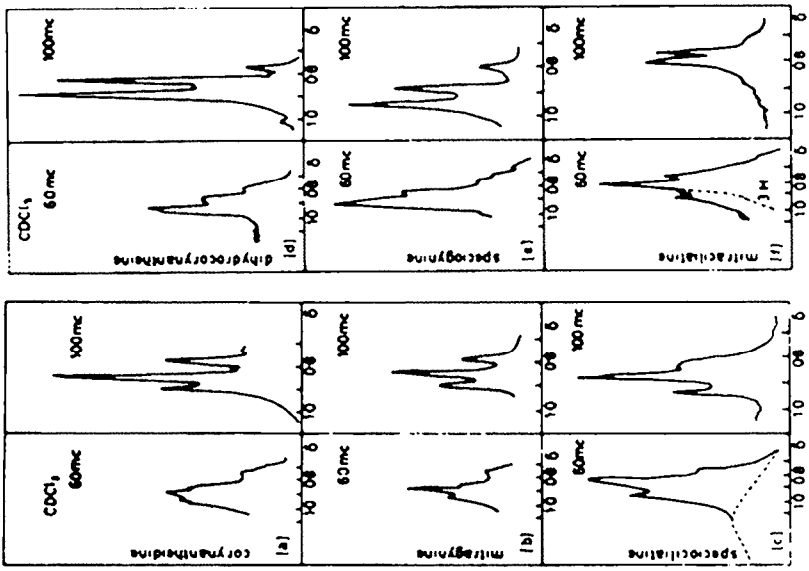


Fig. 1. NMR C19 methyl triplet signal for some corynantheidine-type alkaloids (60 and 100 mc., $CDCl_3$, δ values, ppm from TMS).

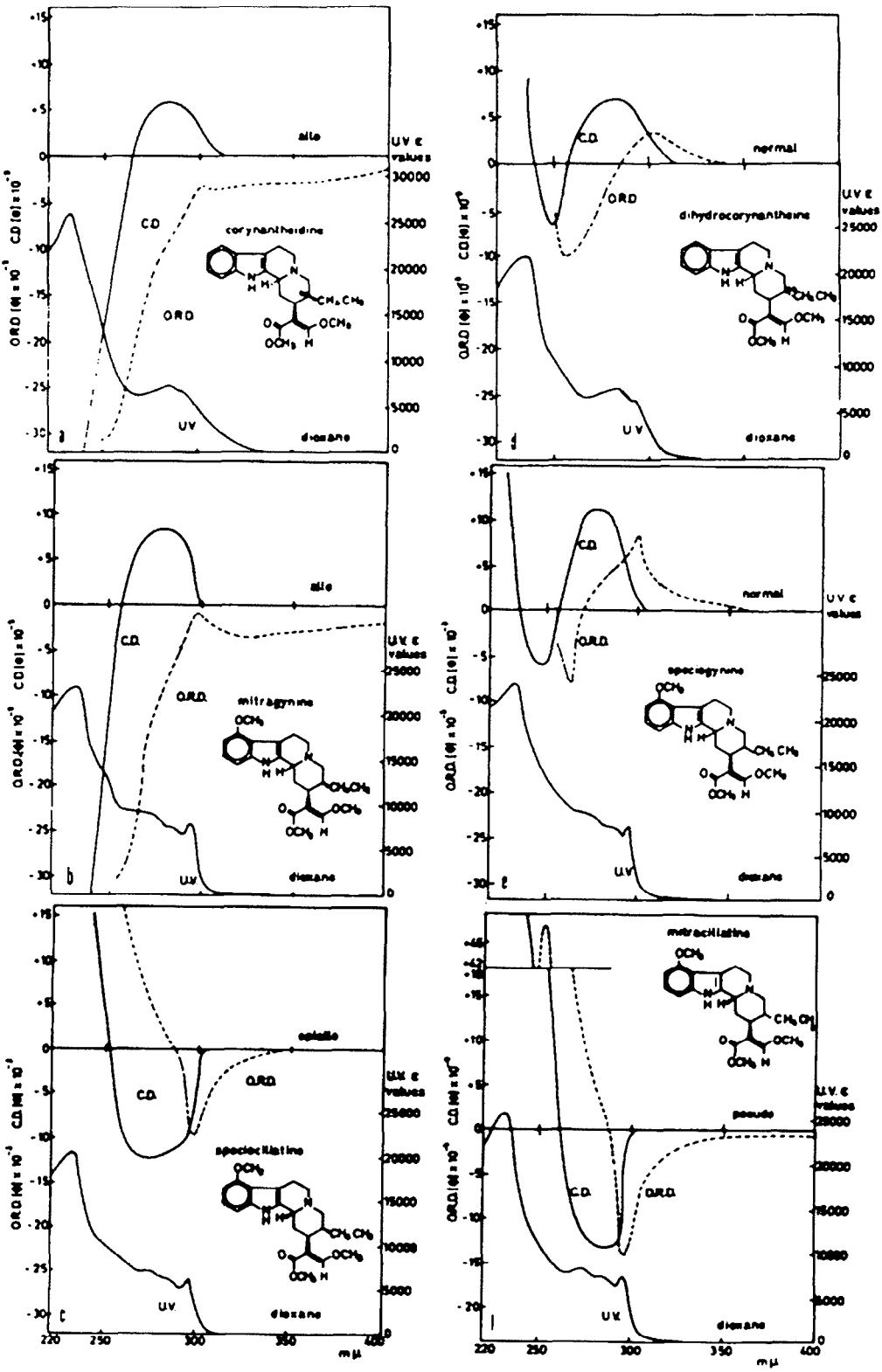


Fig. 3. ORD, CD and UV spectra of some corynantheidine-type alkaloids in dioxane.

it is possible to establish the absolute configuration of any compound of the corynantheidine-type (ring substituted or unsubstituted)* by utilization of measured physical parameters (IR, NMR, CD, ORD) in conjunction with Table 3.

EXPERIMENTAL

IR spectra: Unicam SP 100 (0·5% KCl discs); NMR spectra: either a Varian A-60 or HR 100 using 10% W/V $CDCl_3$ solns (TMS internal ref); UV spectra: a Unicam SP 800 (0·2 cm cell) using the same solns prepared for ORD/CD measurements. CD curves: Roussel-Jouan Dichrograph (1·0, 0·5 and 0·2 cm cells). Due to the unfavourable ratio between UV extinction and CD[θ] the actual measurements of the intensities of the curves varied from only 1–10 mm at sensitivity 1·5. This leads to uncertainty in the absolute magnitude of the [θ] values but there is no uncertainty in

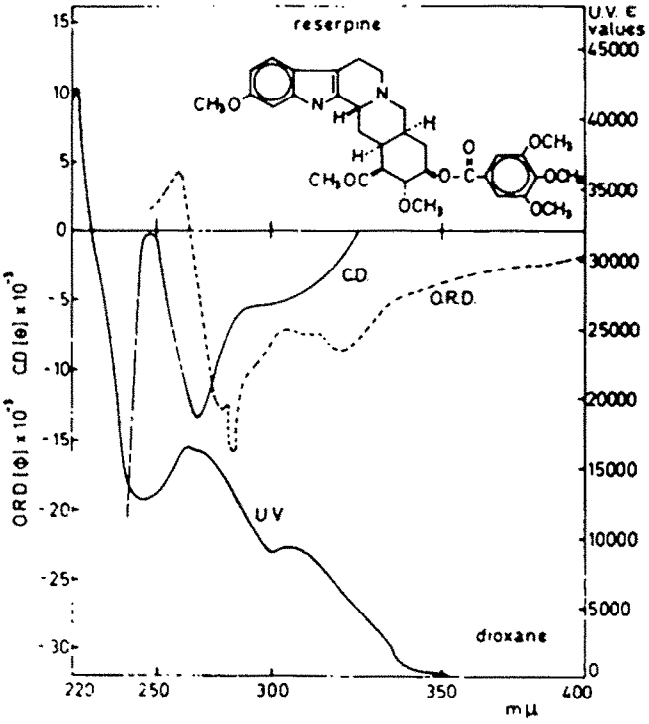


FIG. 4. ORD, CD and UV spectrum of reserpine in dioxan.

the *sign* of the CE. ORD curves: a Bellingham and Stanley Polarmatic 62 equipped with a 250 watt Supersil Xenon lamp with constant N_2 purging, (0·5 cm cell, range: 150 mm = 100 millidegrees).

Preparation of UV/CD/ORD solutions. Approximately 2 mg of sample was accurately weighed on an Oertling 142 microbalance or on a Cahn Electrobalance and placed in a 10 ml volumetric flask. The solutions were made up to volume from a newly opened bottle of spectroscopic grade dioxane (20°).

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* The preferred conformation of corynantheidine-type alkaloids should be invariant of indole ring substitution.