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THE ABSOLUTE CONFIGURATION OF PAYNANTHEINE AND HIRSUTINE

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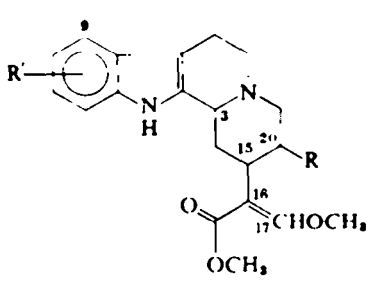
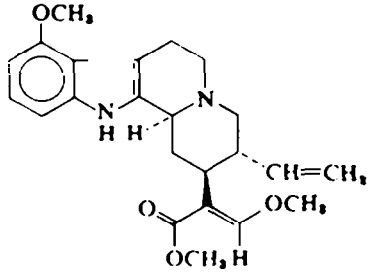
Abstract—Paynantheine is shown to be 9-methoxycorynantheine, *normal* configuration (C15Hα) and hirsutine is shown to be a *pseudo* compound (C15Hα) of the corynantheidine series. Paynantheine, hirsutine and corynantheine have *trans* (methoxy versus carbomethoxy) C16–C17 double bond geometry as demonstrated by NMR data.

PAYNANTHEINE, an alkaloid isolated from the leaves of *Mitragyna speciosa*, has been shown to be a 9-methoxy analogue of the corynantheine-type (I, R′ = 9-OCH_3, R = $CH{=}CH_2$) by analytical and spectral data.[1]



I



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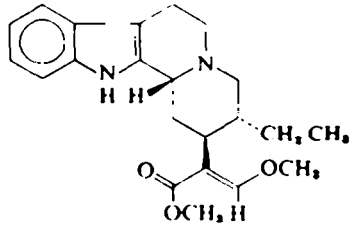

III

It has been demonstrated by NMR data[2,3] that the C16–C17 double bond geometry of corynantheidine-type alkaloids (I, R′ = H or 9-OCH_3, R = Et) is *trans* (methoxy versus carbomethoxy) rather than *cis* as previously proposed[4] for alkaloids of both corynantheidine- and corynantheine-type. The C17 olefinic signal (NMR) for dihydro-

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[1] A. H. Beckett, E. J. Shellard, J. D. Phillipson and C. M. Lee, *J. Pharm. Pharmacol.* **17**, 753 (1965); *Planta Medica* **14**, 277 (1966).

[2] J. A. Weisbach, J. L. Kirkpatrick, K. R. Williams, E. L. Anderson, N. C. Yim and B. Douglas, *Tetrahedron Letters* No. 39, 3457 (1965).

[3] C. M. Lee, W. F. Trager and A. H. Beckett, *Tetrahedron* **23**, 375 (1967).

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

corynantheine[5] (R′ = H, R = Et, *normal*)* appears at 7·40 ppm (δ) while that of corynantheine[5] (I, R′ = H, R = CH=CH_2, *normal*) appears at 7·35 ppm. These data suggest two possibilities. The first is that both alkaloids have the *trans* double bond geometry in which case the vinyl group has little effect on the chemical shift of the olefinic proton. The second is that corynantheine has a *cis* double bond geometry but the vinyl group has a deshielding effect on the olefinic proton large enough to make the olefinic signals[3] of the two compounds almost coincidental. Support for the first, but not the second possibility is found in an examination of Drieding models which indicates that in the preferred conformation of a compound of *normal* configuration,[6] the olefinic proton in both *cis* and *trans* configurations is reasonably far removed from the vinyl group. Therefore any long range shielding effect of the vinyl group on the olefinic proton would be expected to be minimal. Furthermore, dihydrocorynantheine can be obtained by the catalytic reduction of the vinyl group of corynantheine.[7] Isomerization about the C16–C17 double bond is not expected during the course of this reaction. Thus corynantheine should be reassigned the *trans* C16–C17 double bond geometry.

The olefinic proton signal for paynantheine appears at 7·39 ppm (corynantheine, 7·35 ppm) and in line with the above reasoning, paynantheine is assigned the *trans* double bond geometry about C16–C17.

Before firm configurational assignment can be made from physical data alone, the preferred conformation(s) of each configuration must be known.[6] Conformational analysis of corynantheine-type alkaloids (I, R = CH=CH_2) in a manner analogous to that reported for corynantheidine-type alkaloids[6] (I, R = Et) [C20 Et($-\Delta G° = 1·8$ kcal/mole)[8] replaced by C20 vinyl ($-\Delta G° = 1·35$ kcal/mole)[9] in cyclohexane-type compounds] indicates that substitution of a vinyl group for the ethyl group does not change the preferred conformation of a given configuration.

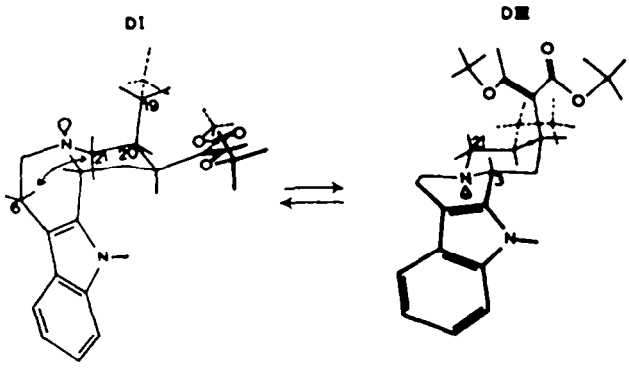
It is interesting to note, however, that the analysis predicts that the conformational equilibrium (75% DI $\leftrightharpoons$ 25% DIII in $CDCl_3$) shown[3] for *epiallo* corynantheidine alkaloids will be shifted further towards the direction of DI (C20 substituent = vinyl) in corynantheine-type alkaloids as an *axial* vinyl group is relatively more favourable than an *axial* ethyl group.[8,9]

The IR spectrum of paynantheine shows C3H *trans* bands, and a multiplet characteristic of a *cis* C3H is not observable in the NMR spectrum; thus the preferred conformation of paynantheine is one where the C3H is *trans* to the nitrogen lone pair.[1]

* Terminology for the configurations is as follows:

Configuration	C3H	C15 H	C20 H
Normal	α	α	β
Pseudo	β	α	β
Allo	α	α	α
Epiallo	β	α	α

[1] M. F. Bartlett, R. Sklar, W. I. Taylor, E. Schlittler, R. L. S. Amai, P. Beak, N. V. Bringi and E. Wenkert, *J. Amer. Chem. Soc.* **84**, 622 (1962).
[6] W. F. Trager, C. M. Lee and A. H. Beckett, *Tetrahedron* **23**, 365 (1967).
[7] P. Karrer, R. Schwyzer and A. Flam, *Helv. Chim. Acta* **35**, 851 (1952).
[8] N. L. Allinger and L. A. Frieberg, *J. Org. Chem.* **31**, 894 (1966).
[9] R. J. Ouellette, K. Liptak and G. E. Booth, *J. Org. Chem.* **31**, 546 (1966).



Since the preferred conformation of the configurations of both corynantheine- and corynantheidine-type alkaloids are the same, conformational analysis[3,6] indicates that paynantheine must have either the *normal* or *allo* configuration. The fact[1] that the vinyl proton multiplets of paynantheine correspond in chemical shift, multiplicity and integral with the vinyl signals of corynantheine (I, R′ = H, R = CH=CH$_2$, *normal*) suggests that paynantheine also has the *normal* (C3Hα, C15Hα, C20Hβ or C3Hβ, C15Hβ, C20Hα) configuration.

A firmer basis for configurational assignment rests upon comparison of the ORD/CD curves of paynantheine (Fig. 1a) with those displayed[3] by the corynantheidine-type alkaloids (I, R′ = 9-OCH$_3$, R = Et) having the *normal* and *allo* configuration (speciogynine and mitragynine respectively.*) The ORD/CD curves of paynantheine (Fig. 1a) correspond to those of speciogynine[3] (*normal*) and are different from those of mitragynine[3] (*allo*). Since the sign of the Cotton effects at 270–300 mμ of paynantheine, like those of speciogynine and dihydrocorynantheine, are positive, paynantheine must have the *normal* configuration with the C15Hα (II).

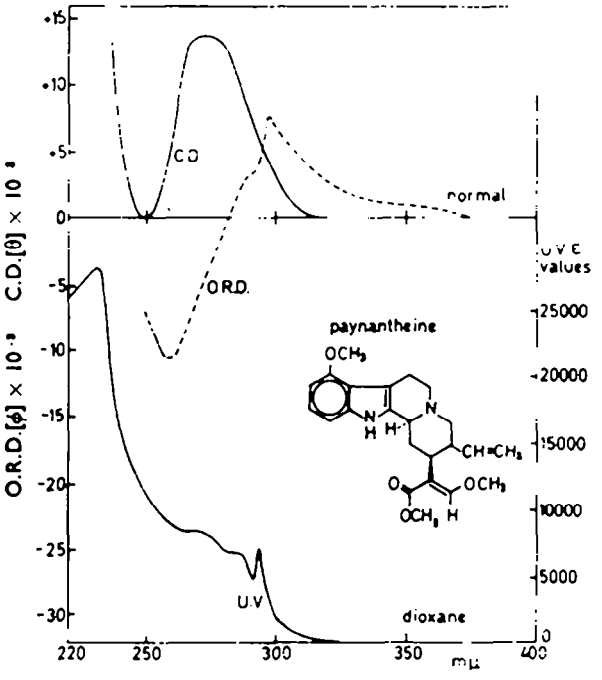
Finally, chemical confirmation of the assigned configuration has been obtained by hydrogenation of paynantheine. Both thin-layer and gas chromatography indicate that the reduction product of paynantheine is speciogynine and not mitragynine.

Hirsutine, an alkaloid isolated from the leaves of *Mitragyna hirsuta* has been shown to have a corynantheidine-type structure (I, R′ = H, R = Et).[10] A *trans* C16–C17 double bond geometry is indicated by the position of the olefinic proton signal at 7·35 ppm (see discussion Ref. 3). A C3H *cis* to the nitrogen lone pair is demonstrated by the absence of *trans* CH IR bands and the presence of a one-proton *cis* C3H multiplet in the NMR spectrum.[3,6,10] This data in conjunction with the conformational analysis of corynantheidine-type compounds[3,6] indicates that hirsutine can only be a *pseudo* or *epiallo* compound; furthermore the compounds of type I (R′ = H, R = Et) having the *allo* and *normal* configuration are known (corynantheidine and dihydrocorynantheine respectively).[3]

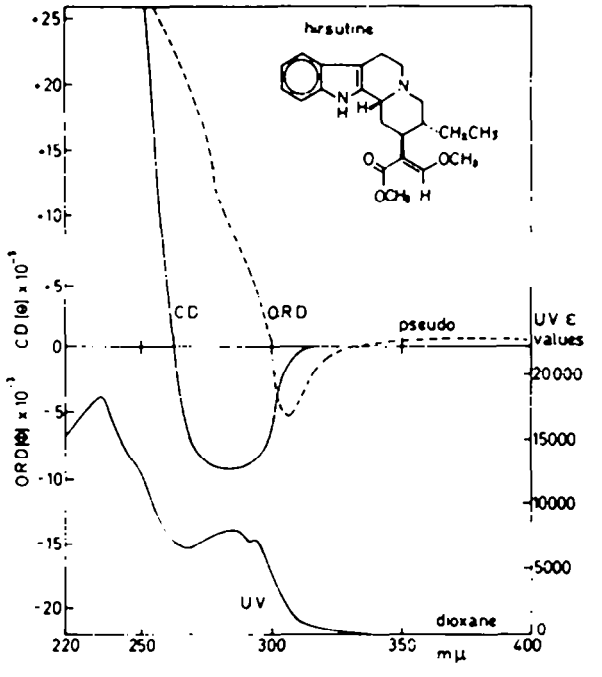
A *pseudo* or *epiallo* compound of corynantheidine-type can be distinguished by two criteria in the NMR spectrum:[3,6] (1) position of the *cis* C3H multiplet and (2) resolution of the C19 methyl triplet. In hirsutine, the *cis* C3H multiplet appears at

* Substitution of vinyl for ethyl should not have a pronounced effect on the general shape of the curves.

[10] E. J. Shellard, A. H. Beckett, P. Tantivatana, J. D. Phillipson, and C. M. Lee, *J. Pharm. Pharmac.* **18**, 553 (1966).



1a.



1b.

FIG. 1. UV, ORD and CD spectra of paynantheine and hirsutine in dioxane.

4·45 ppm[10] and the resolution of the methyl triplet signal is unsymmetrical (Fig. 2) thus indicating that the alkaloid possesses the *pseudo* (C3Hβ, C15Hα, C20βH or C3Hα, C15Hβ, C20Hα) configuration.

The ORD/CD curves of hirsutine (Fig. 1b) show negative Cotton effects (270–300 mμ) like those of mitraciliatine (I, R′ = 9-OCH$_3$, R = Et, *pseudo*).[3] Hence hirsutine (III) has the *pseudo* configuration with the C15Hα and is the non-methoxylated analogue of mitraciliatine.

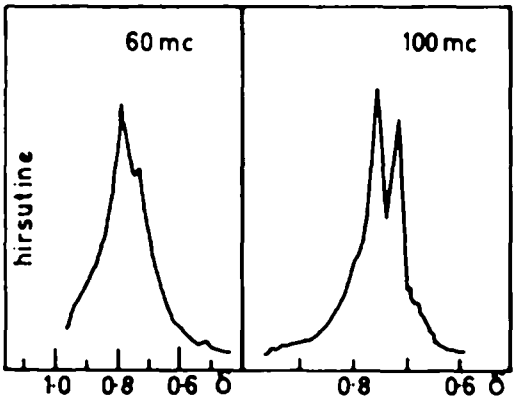


FIG. 2. C18 methyl triplet resolution of hirsutine (60 and 100 mc NMR in CDCl$_3$)

EXPERIMENTAL

All ORD, CD, UV, IR and NMR spectra were measured as previously described.[3] Hydrogenation of paynantheine (14 mg) was carried out in AcOEt (2 ml) in the presence of 5% Pd on BaSO$_4$ (25 mg). After 1 hr the soln was filtered and compared on TLC plates with authentic samples of paynantheine, mitragynine and speciogynine. In the 3 systems used* the reaction mixture showed 2 spots (Dragendorff reagent) one of which corresponded to paynantheine while the other corresponded to speciogynine. The reaction mixture was also injected on a F11 gas chromatograph† [6 ft, glass column (O.D. $\frac{1}{4}$ inch) packed with 2% SE 30 on acid washed DMCS treated Chromosorb G (80–100 mesh); oven temp 230°, injection temp 325°; H_2-20 psi. N_2-30 psi, air-35 psi]. A two-component mixture (a) 52·5 min R_t; (b) 49·0 min R_t was indicated, with the a/b ratio (peak heights) being 1·65. Component (a) was identified as speciogynine as addition of authentic speciogynine to the reaction mixture resulted in increased ht of (a)†. Similarly paynantheine was identified as component (b).

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* TLC hR_f Reference Values[11]

	Paynantheine	Mitragynine	Speciogynine
Silica gel–ether	48	70	35
Silica gel–CHCl$_3$: acetone, 5:4	64	70	52
Alumina–CHCl$_3$: benzene, 1:1	39	62	33

† GLC R_t Reference Values (above conditions) 49·0 min 47·5 min 52·5 min

[11] J. D. Phillipson and E. J. Shellard, *J. Chromat.* in press.